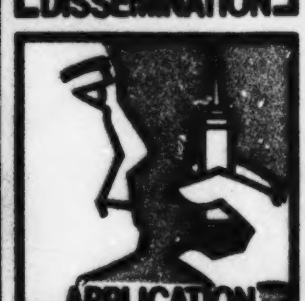
NCI/ICRDB/OK-78/03

HE 20.3173/3:OK-78/3
NTISUB/D/229-004




7 1978

ONCOLOGY OVERVIEW

COMPLETED

ORIGINAL

# SELECTED ABSTRACTS

# ON

# THE ROLE OF PSYCHOLOGICAL FACTORS IN THE ETIOLOGY OF CANCER

SEPTEMBER 26, 1978

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service • National Institutes of Health •
National Cancer Institute

A SERVICE OF THE
INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB)

36

*Oncology Overviews* are a service of the International Cancer Research Data Bank (ICRDB) program of the National Cancer Institute. Each *Oncology Overview* represents a survey of the literature associated with a selected area of cancer research. It contains abstracts of articles which have been selected and organized by researchers associated with the field. The purpose of this *Oncology Overview* is to facilitate and promote the exchange of information between cancer scientists by keeping them aware of literature related to their research being published by other laboratories throughout the world.

The material published in *Oncology Overviews* is obtained from Cancerline, an online cancer information system created by the ICRDB program in cooperation with the National Library of Medicine. Abstracts from the Cancerline data base, which is updated monthly with new articles abstracted from more than 1500 journals, can be retrieved via online computer terminals at more than 500 locations in the U.S. and other countries. Any organization linked to the Medlars Medline system at the National Library of Medicine has access to the Cancerline data base.

This *Oncology Overview* is sent automatically to researchers in the subject area who are identified on the basis of current research project descriptions submitted to an ICRDB-supported Current Cancer Research Project Analysis Center (CCRESPAC). We encourage all cancer researchers to provide a complete and current project description to CCRESPAC. If you have not recently supplied such a description to an agency providing input to this program (ie, NIH, American Cancer Society, Cancer Center Directors, etc.), you may obtain forms and additonal information about data input from the ICRDB program office address listed below.

*Oncology Overviews* may also be obtained by any requestor at modest cost from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, Virginia 22161, USA.

This *Oncology Overview* is prepared for the ICRDB program by the Cancer Information Dissemination and Analysis Center (CIDAC) for Carcinogenesis Information. Future *Overview* editions depend on user needs and satisfaction. If you have favorable comments on this *Oncology Overview*, or you would like to receive other ICRDB publications and learn about other ICRDB information services, please contact:

ICRDB Program Office
National Cancer Institute
Blair Building, Room 114
8300 Colesville Road
Silver Spring, Maryland 20910, USA

EACH RESEARCHER RECEIVING THIS PUBLICATION IS URGED TO CIRCULATE THIS *OVERVIEW* TO COLLEAGUES, CO-WORKERS, AND OTHERS WHO ARE ENGAGED IN PROJECTS RELATED TO THE AREA COVERED BY THIS PUBLICATION.

# TABLE OF CONTENTS


ABSTRACT NUMBER

INTRODUCTION

EDITORIAL COMMENTARY

I. PSYCHOSOCIAL FACTORS IN THE OCCURRENCE OF HUMAN CANCER

A. Association of Cancer Occurrence with Emotional or Mental Stress ..... 1-13

B. Cancer Occurrence in Relation to Marital Status ..... 14-21

C. Cancer Occurrence in Relation to Behavioral and Cultural Values ..... 22-25

II. THE INCIDENCE OF CANCER IN PSYCHIATRIC PATIENTS ..... 26-28

III. PERSONALITY TRAITS ASSOCIATED WITH THE OCCURRENCE OF HUMAN CANCER

A. Association Depression and Other Affective Disorders ..... 29-36

B. Personality Traits Associated with the Occurrence of Human Cancer ..... 37-44

C. Psychological Testing in the Prediction of Human Cancer Risk ..... 45-54

IV. ENDOCRINOLOGICAL AND IMMUNOLOGICAL CORRELATES OF PSYCHOLOGICAL FACTORS AND CANCER ..... 55-66

V. EXPERIMENTAL STUDIES ON THE PHYSIOLOGICAL EFFECTS OF STRESS IN RELATION TO CANCER INDUCTION

A. Hormonal and Immunological Effects of Environmental Stress in Animals ..... 67-79

B. Modification of the Effects of Environmental Stress by Fat-Soluble Vitamins ... 80-87

VI. THE ROLE OF ENVIRONMENTAL STRESS IN THE EXPERIMENTAL INDUCTION OF CANCER

A. Interaction of Chemical or Physical Carcinogens and Stress: Inhibition of or No Effect on Tumor Growth ..... 88-100

B. Interaction of Chemical or Physical Carcinogens and Stress: Enhancement of Tumor Growth ..... 101-106

C. Effect of Stress on the Growth of Transplanted Tumors ..... 107-115

D. Effect of Stress on the Growth of Virus-Induced or Spontaneous Tumors ..... 116-125

SUBJECT INDEX

AUTHOR INDEX

# INTRODUCTION

This ONCOLOGY OVERVIEW on the role of psychologic factors in the etiology of cancer is comprised of abstracts of articles published in 1970-1977 (with some dating back to 1963) that are available in the CANCERLINE computerized data base. The strategy used for the on-line data base is available on request from the CIDAC and can be entered at any MEDLARS/MEDLINE terminal system in order to update the references in this area.

The scope of this OVERVIEW covers all aspects of the relationship between carcinogenesis and psychological states or emotional stress. Included are epidemiological associations of psychosocial factors and personality traits with various cancers, psychological testing for cancer risk, and the incidence of cancer in psychiatric patients, as well as the role of physiological mechanisms in the promotion of cancer: Experimental studies covering the effects of psychological stress on tumor induction or enhancement and physiological effects related to cancer induction are also included.

This OVERVIEW was prepared by Kathleen N. Weiss (editor), John S. Krebs, William E. Davis, Jr., and Barbara Thompson of the CIDAC staff, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025. The consulting reviewer was Dr. Gordon T. Pryor, SRI International.

## EDITORIAL COMMENTARY

There is evidence that poor emotional outlet, depression, and earlier personal loss are common threads that run through the life histories of cancer patients. A research difficulty is presented, however, in that some of these characteristics may also be secondarily related to the diagnosis of cancer.

The bulk of the evidence that psychological factors are important in the etiology of cancer consists of retrospective case controlled studies comparing the personality traits of cancer patients with noncancer patients or healthy people, with the probability that such personality traits antedated the appearance of the cancer. The question of whether personality or psychodynamic conflicts lead to the expression or promotion of cancer presents a complex research problem. The most definitive type of study, selecting people on the basis of personality factors and determining success in predicting subsequent cancer, has not been done.

The evidence from experimental work with rodents suggests that psychological of physiological stress may possibly act through the mechanism of depressing the immunological surveillance system and/or altering the biochemical or hormonal milieu, to allow the initiation or more rapid progression of cancer.

Many studies suggest that certain personality types showing tendencies to abuse alcohol, cigarettes or drugs are 'cancer prone' personalities. These studies were not included here because it is difficult to isolate the 'direct' effect of these carcinogenic agents on the potential for cancer.

The extensive evidence that chemical, physical, or viral agents are causative factors in the etiology of cancer does not contradict the hypothesis that psychobiological mechanisms may predispose or interact as causative factors. Psychobiological factors are compatible with a multifactorial model in the etiology of cancer.

### SUPPLEMENTARY REFERENCES

The literature on the role of psychological factors and stress in the etiology of cancer is quite extensive. The following supplementary references may be helpful to the reader:(1) First Conference on Psychophysiological Aspects of Cancer. Ann. N.Y. Acad. Sci. 125(3), 1966.(2) Second Conference on Psychophysiological Aspects of Cancer. Ann. N.Y. Acad. Sci. 164(2), 1969.(3) Stress, Psychological Factors, and Cancer, J. Achterberg, O.C. Simonton, and S. Matthews-Simonton, eds. New Medicine Press, Fort Worth, Texas, 1976.(4) M. Stein, R.C. Schiavi, and M. Camerino, Influence of Brain and Behavior on the Immune System. Science 191, 435-439, 1976.(5) J.G. Rabkin and E.L. Struening, Life Events, Stress, and Illness. Science 194, 1013-1020, 1976.(6) C. Holden, Cancer and the Mind: How Are They Connected? (News and Comment). Science 200, 1363-1369, 1978.(7) F.G. Surawicz, D.R. Brightwell, W.D. Weitzel, and E. Othmer, Cancer, Emotions, and Mental Illness: The Present State of Understanding. Am. J. Psychiatry 133, 1306-1309, 1976.(8) C.B. Thomas and R.L. Greenstreet, Psychobiological Characteristics in Youth as Predictors of Five Disease States: Suicide, Mental Illness, Hypertension, Coronary Heart Disease, and Tumor. Johns Hopkins Med. J. 132, 16-43, 1973.

# I. PSYCHOSOCIAL FACTORS IN THE OCCURRENCE OF HUMAN CANCER

## A. Association of Cancer Occurrence with Emotional or Mental Stress

### 1. PSYCHOSOCIAL STRESS AND CANCER (MEETING ABSTRACT). (PP. 42-43)

Baltrusch HJ

Intnatl Psychosom and Cross-Cult Leuk Proj, D-2900 Oldenberg, West Germany

Third International Symposium On Detection And Prevention Of Cancer. 1976.

During the past two decades systematic psychosomatic studies have been undertaken in order to evaluate the importance of psychosocial stress in the development and course of cancer. At present, more than 8,000 patients with different lesions have been studied by a number of scientists by means of individual, retrospective, group and prospective investigations. In these studies, it could be demonstrated that in the majority of patients clinical manifestation of malignancy occured during a period of severe and intensive life stress involving frequently loss, separation and other bereavements. The basic psychological orientation of the cancer patient and the peculiarities of the personality of cancer prone individuals are outlined. Recent group investigations in breast and cervix cancer patients were able to demonstrate first results with regard to the identification of persons being at a high risk by means of psychological techniques. Delay of diagnosis and treatment is not only dependent upon socioeconomic factors, but also on the rigid and secretive personality of cancer patients. Further investigations were able to show that also clinical prognosis seems to be influenced by psychosocial factors. A number of psychologic variables have been elucidated with regard to good and bad prognosis of cancer. Attention is given to psychophysiologic animal experiments showing the effect of psychosocial stress on tumorigensis. (Author Abstract)

### 2. PSYCHOSOMATIC FACTORS AND TUMOUR GROWTH. (PP. 193-203)

Stoll BA

Risk Factors in Breast Cancer. Edited by BA Stoll Chicago William Heinemann Medical Books, New Aspects Of Breast Cancer, vol. 2, 1976.

There have been a number of recent reports suggesting that emotional stress in women may influence the development and growth of breast cancer. The hypothalamopituitary pathway could mediate a cerebral influence on growth. The growth pattern of breast cancer shows a remarkable diversity and is thought to result from interaction between the aggressive potential of the tumor cells and host factors, which may well include psychosomatic factors. Prolactin, growth hormone, and gonadotropin levels can be increased markedly by emotional as well as somatic stress. A higher corticosteroid production has been noted in breast cancer patients who are apprehensive or depressed. An indirect measure of emotional stress derived from the patient's use of tranquilizers, antidepressants, sedatives, or hypnotics was made in a series of 250 patients. Their drug usage in the 12 mo prior to diagnosis was similar to that of women in the general population. However, after diagnosis, the overall drug usage was two to three times higher in the general population than in women. Of five groups of patients distinguished, those with evidence of metastases beyond the axilla at the time of diagnosis and those showing evidence of recurrence or metastases within 12 mo of radical treatment included the highest proportion of those who, in the past, required medication for emotional distress. If a relationship between the persistent emotional stress and an increased rate of breast cancer growth should be confirmed, it does not follow that it is one of cause and effect; they both may arise from a common basis.

### 3. STRESS IN THE AETIOLOGY OF BREAST CANCER.

Lask M

Med World (Lond); 98(3):197-200 1963

The author discusses the importance of stress in the etiology of carcinoma of the breast as seen in 31 female patients (aged 49-85; 24 were post-menopausal) and 1 male patient (aged 46). Of these patients, 27/32 (84%) had suffered prolonged periods of emotional stress prior to the onset of malignancy. Case histories of 4 female patients, selected at random, are cited as examples. The author concludes that chronic, severe emotional stress (especially if accompanied by prolonged physical stress) may be a factor, and even a decisive one, in the etiology of mammary cancer, while acute stress or stress occurring over short periods of time is more likely to predispose to heart attacks or some types of skin disorder. Suggested as a minimum period of chronic stressing for induction of mammary cancer is 5-7 yr. The author also concludes that personality type is not a factor in carcinogenesis.

### 4. THE SEARCH FOR WOMEN AT HIGH RISK. (PP. 207-225)

Leis HP, Raciti A

Risk Factors in Breast Cancer. Edited by BA Stoll Chicago William Heinemann Medical Books, New Aspects of Breast Cancer, vol. 2, 1976.

Both experimental and clinical observations indicate that the development of breast cancer is not a chance event that occurs randomly throughout the population. Certain women are in a high risk group. The major predictors of high risk include sex, age, familial history of breast cancer, parity, and previous cancer in one breast, and the precancerous type of fibrocystic disease. Over 99% of the cases occur in women, 75% in those over 40 yr. The hereditary forms are more frequent than is generally suspected. They have an early age at onset, tend to be bilateral or multiple, and seem to fit the two-step mutational concept. The risk of breast cancer in women with one or two children is 1.5 to 2.0 times that of women with three or more children. Although parity before the age of 25 exerts a definite protective influence, pregnancy after 35 may well carry a risk greater than that for nulliparous women. The risk of developing cancer in the second breast after the first has been removed is about five times greater than the risk of initial breast cancer in the general population. The presence of fibrocystic disease of the breast also increases the risk; in fact, there may be a common hormonal predisposition for both diseases. Prominent predictors of high risk include viral factors, immunological factors, genetic factors, radiation exposure, cancer in other organs, alteration in the hormonal milieu (including estrogen), castration and menstrual activity, and etiocholanolone and/or androsterone excretions. Possible predictors of high risk of breast cancer have varied statistical significance. They include high dietary fat, chronic

psychogenic stress, hormone administration, trauma, chemical agents, hypothyroidism, living in the Western Hemisphere, upper socioeconomic status, living in a cold climate, being of the white race, and being Jewish.

**5. TRAUMA AND CANCER.**

Tashima C
St. Francis Hosp., Honolulu, Hawaii
Lancet: 7880:590-591 1974

A case report of a 49-yr-old Korean woman who died with carcinoma of the right breast is presented. A rather unusual sequence began with hysterectomy and oophorectomy, progressing rapidly to coronary-artery disease, and terminating in death from breast cancer within 28 months. Conjugated estrogenic hormones ('Premarin') had been administered. The author concludes that the time course of this case suggests that cancer had already been initiated in the past and that the recent events (hormonal changes, injuries, stresses, and metabolic disturbances) had enhanced the growth and spread of the cancer. It is reported that trauma may act as a co-carcinogen, though there is no evidence that single uncomplicated trauma causes cancer. Trauma does influence the site of blood-borne metastases.

**6. RISK FACTORS ENCOUNTERED IN CASES OF CERVICAL CANCER AND IN PRECARCINOMATOUS CONDITIONS.**

Kralova A
Gynek.-porod. klinika ILF Praha, Prague, Czechoslovakia
Cesk Gynekol; 40(7):551-559 1975

The occurrence of risk factors responsible for the development of cervical cancer was studied in 150 women (average age 46.2 yr) with uterine cervical carcinoma, in 100 women (average age 37 yr) with conditions precancerous in the strict sense, and in 150 female controls. Educational level was distinctly higher in the precancerous group than in the others. The age of onset of regular sexual activity was 18-19 yr in the majority of the carcinoma group, 20 yr in most of the precancerous group, and 20-21 yr in the majority of controls, while the age of the first pregnancy was most often 18-19 yr in the carcinoma group, 21 and 23 yr in the precancerous group, and 23 yr in the controls. Differences in the number of births were found between the carcinoma group and the other two groups, and the precancerous group had more sexual partners. No significant differences in nervous and emotional instability were found among the studied groups, but the carcinoma group predominated in the category of instability associated with psychological trauma. One-third of the precancerous group were heavy smokers, compared with one-fourth of the carcinoma group. Although the above-mentioned differences were found at varying levels of statistical significance, no reliable predisposing factors were proved in the majority of those in the precancerous and carcinoma groups. Thus, no definite risk groups for cervical cancer could be established.

**7. ETIOLOGIC SURVEY OF CARCINOMA OF UTERINE CERVIX.**

She Ming-P'eng, Ch'eng Feng-Ling, Liu T'ung-Hua, Ts'ai Hai-Ying, Liu Chih-Ming, Wu Ai-Ju
Dept. Path., Inst. Exp. Med., Peking, China
Chin Med J ; 82(1):39-45 1963

The results of a statistical survey showed a significant correlation among 278 patients with cervical cancer (mostly squamous-cell), compared to 319 controls, and the factors of early marriage (48.5%:35.2%), early childbearing (28.0%:12.5%), multiple pregnancies (49.1%:35.4%), multiparity (43.0%:27.6%), frequent parturition (39.0%:22.7%), phimosis of partner (31.0%:11.7%), and emotional stress (47.5%:32.0%). Many carcinoma patients had a combination of 2 or more endogenous and/or exogenous factors, as compared to controls (67.7%:33.7%).

**8. THE RELATION OF PSYCHOLOGICAL STRESS TO ONSET OF MEDICAL ILLNESS.**

Hurst MW, Jenkins CD, Rose RM
Boston Univ. Medical Sch., Boston, MA 02118
Annu Rev Med; 27:301-312 1976

The relation between psychological stress and the onset of medical illness is discussed. The relation of psychological stress to the onset of cardiovascular and neoplastic disease is highlighted. Each of the disease categories is considered from the two approaches to a definition of psychological stress: emotional responses and life-event stimulus situations. Either newly-evidenced anxiety and depression or exacerbated chronic anxiety and depression may heighten the probability of onset of coronary heart disease and particularly of angina pectoris. However, the evidence does not distinguish whether these manifestations of psychological stress are long-term precursors or short-term precipitants of coronary heart disease. From the point of view of psychological stress in the onset of cancer, the results of the prospective and carefully controlled studies contradict the clinical and retrospective uncontrolled studies. In the former type of study cancer patients had significantly lower neuroticism scores than other patient groups as well as normal controls. In the latter type of studies loss and depression seemed significant antecedents to the onset of cancer. For lung and breast cancers there has been a lack of definitive evidence that increased life-event stress plays a role in the onset of the neoplasm, while there has been some consistent suggestion that life-event stress may be related to the onset of cervical cancer, leukemia, and lymphoma. Suggestions for research and practice are offered. Studies on the relationship of psychological stress to the onset of medical illness have suggested a complex interaction of factors rather than a simple causal link. The results suggest a strong role for psychiatric consultation and liason in the rehabilitation of cardiovascular and neoplastic patients; they do not, however, suggest a means of prevention.

**9. A PSYCHOPHYSIOLOGIC ANALYSIS OF CERTAIN FUNCTIONS OF HIGHER NERVOUS SYSTEM ACTIVITY IN INFANTS, CHILDREN AND EARLY ADOLESCENTS WITH LEUKOSES AND OTHER MALIGNANT DISORDERS OF THE HEMATOPOIETIC, LYMPHATIC AND RETICULOENDOTHELIAL SYSTEM.**

Baltrusch HJ
19 Babenend St, Oldenberg 29, Oldenberg, West Germany
Act Nerv Super (Praha); 5(4):373-390 1963

Reported is an experimental psychological study of 60 patients with leukemia and allied disorders, aged less than 1 to 14 (av, 6.7) yr. (36 boys and 24 girls). As to type, 40 had acute stem-cell, 2 had eosinophilic, 1 had chronic myeloid leukemia; 4 had leukemiform reticuloses; 2 had lymphosarcoma; 3 had reticulum cell sarcoma; and 5 had Hodgkin's disease. Three had leukemias (type not stated) associated with trisomal feeblemindedness. Included in the evaluation procedures were both child and parent interviews, Rorschach's Test, the TAT, the CAT, the Machover technic, et al. The author concludes that children and early adolescents who develop leukemia or allied disorders have been exposed to a very much greater range and intensity of psychosocial stresses than normal children; and that the course of the disease is 'directly dependent' upon the degree of continuing stress in the psychosocial environment. He states that emotional stress, negative emotion, and/or functional disturbance of nervous reflex activity weaken the organism's resistance in a non-specific way and initiate or foster development of the malignant process. (See also CRA 2(2):#165, 1964).

**10. GASTRIC ULCER, DUODENAL ULCER AND GASTRIC CARCINOMA: A CASE-CONTROL STUDY OF CERTAIN SOCIAL AND ENVIRONMENTAL FACTORS.**

Gillies M, Skyring A
Roy. Prince Alfred Hosp., Sydney, Australia
Med J Aust; 2(25):1132-1136 1968

Interviews designed to obtain information about more than 40 genetic and environmental factors (including socioeconomic and marital status, occupation, family histories of peptic ulcer, smoking, alcohol consumption, and consumption of drug preparations with or without aspirin) were obtained from 150 patients with peptic ulcers (stomach in 100/150, duodenal in 50/150), 50 patients with stomach cancer, and equal numbers of age- and sex-matched controls without histories or symptoms of upper g.i. disease (not excluding patients taking analgesic or anti-inflammatory agents, with or without aspirin). The patients with stomach cancer and duodenal ulcers did not differ from any of the control groups in any of the factors studied, although the patients with stomach ulcers differed from the control groups in several parameters (including smoking, alcohol and aspirin consumption, family ulcer histories, and parameters indicating mental stress).

**11. SOME PSYCHOLOGICAL AND CLINICAL BACKGROUND DATA ON THE ENVIRONMENTAL FACTORS WHICH AFFECT TUMOR FORMATION, CONSIDERED FROM THE STANDPOINT OF THE MEDICAL PRACTITIONER.**

Nemeth G, Oo M
5 Gyori St., Budapest, Hungary
Z Psychosom Med Psychoanal; 9(4):262-265 1963

In order to evaluate clinical and psychosocial factors conducive to the development of cancer, 100 patients (28 males, 72 females) with various malignant diseases were interviewed. The malignancies included carcinomas of the breast (22), female genitalia (21), g.i tract (17), lungs (6), bladder (4), prostate (3), thyroid (4); 6 leukemias, 4 Hodgkin's disease, and 13 in various sites. In 22 patients, a familial predisposition seemed likely. Manifestation of the tumor was preceded in 21 by infectious diseases, in 9 by mechanical trauma, in 31 by nonmalignant disorders involving the same organ. Also discussed is the role of psychological trauma, physical and emotional exhaustion due to stress and overwork and depressive tendencies; 49/100 patients were rather optimistic.

**12. BIOLOGY AND CYTOLOGY OF LUNG CANCER.**

Sirtori C
Acta Ginecol; 20(1):37-52 1968

Possible roles of radiation exposure, chemicals (smoking, air pollution, chromium, nickel, asbestos, etc), viruses, pre-existing conditions (vitamin A deficiency, pulmonary scars, benzpyrene hydroxylase deficiency, etc), genetic factors and psychological stress on the etiology of lung cancer in man are discussed.

**13. SMOKING AND CANCER.**

Burch P
The General Infirmary, Leeds, England
New Sci; 62(892):41 1974

In 20 countries the association between death rates for lung cancer and per capita cigarette consumption are not significant for women and only weakly positive for men. In reviewing the evidence as received from necropsy series, the vast majority of the recorded increase in lung cancer of late has been due to changes in the level of diagnosis. It is suggested that genetic factors may determine the population susceptible to this disease. The hypothesis that stress might act in the manner of a precipitating carcinogen must be considered but is difficult to verify.

## B. Cancer Occurrence in Relation to Marital Status

**14. EPIDEMIOLOGY OF BREAST CANCER IN ALBERTA 1971-1973. (MEETING ABSTRACT).**

Lees AW, Bako G
Dr. W. W. Cross Cancer Inst, Edmonton, Alberta, Canada T6G 1Z2.
Proc Am Soc Clin Oncol; 18:325 1977

During 1971 to 1973, an epidemiological study was conducted on 11,326 patients attending the 3 Alberta cancer clinics, including 1,305 breast cancer patients. These represent 90% of breast cancer registrations on the Alberta Cancer Registry. Data was collected by nursing and admissions staff using a questionnaire-interview. Using the age adjusted indirect method of standardization, incidence rates were calculated showing that breast cancer incidence was significantly higher (p less than 0.05) in 1 town and lower in two as compared to the overall Alberta incidence rates. Demographic analysis by census divisions shows a higher incidence in the urban than rural districts. Significant differences between marital status categories occurred for women in the age group 40-49 (p less than 0.001) but not for women 30-39 and 50-59. Comparison of the divorced category with the three other groups (single, married, widowed), demonstrated a difference with the 40-49 category (p less than 0.001) and the 50-59 (p less than 0.02) but not the 30-39 age group. Consideration of differences in breast cancer incidence between the 3 groups for each of the marital status categories gave significant differences across ages for divorced women (p less than 0.001) and single women (p less than 0.01) but not married or widowed women. It can be concluded that 40-49 year old divorced and 50-59 year old single women are at a higher risk than married or widowed women 30-59 years old. (Author Abstract)

**15. CARCINOMA OF THE CERVIX - AN EPIDEMIOLOGICAL PERSPECTIVE. (PP. 3-15)**

Clarke M
Gynaecological Malignancy: Clinical and Experimental Studies. Brush MG, Taylor RW, ed. Baltimore, The Williams and Wilkins Co., 1975.

Cancer of the cervix is a relatively uncommon cause of death but it does bring a heavy toll in middle-aged women, accounting for 4% of all deaths in the age group 45-64. Women of the lower socioeconomic classes and women who are divorced or widowed experience higher death rates from the disease than women in the upper social classes and women who never married. The standardized mortality ratios for social classes I to V are 34, 64, 100, 116, and 181, respectively. Other factors associated with cervical cancer include age at first coitus and multiplicity of sex partners. There appears to be a close relationship between herpes simplex virus type 2 and cervical cancer. The screening for cervical cancer by cervical smears remains of unproved effectiveness for reducing mortality. Attendance for smear taking is poor among women of lower socioeconomic status, who are at high risk, and there is considerable disagreement among pathologists on the classification of smear specimens, resulting sometimes in inappropriate treatment.

**16. CERVICAL CANCER IN YUGOSLAVIA. II. EPIDEMIOLOGIC FACTORS OF POSSIBLE ETIOLOGICAL SIGNIFICANCE.**

Kessler II, Kulcar Z , Zimolo A, Grgurevic M, Strand M, Goodwin BJ
Johns Hopkins U. Sch. Hyg. Public Hlth., Baltimore, Md.
J Natl Cancer Inst; 53(1):51-60 1974

Epidemiologic factors of etiologic significance were sought in a case-control study of cervical cancer among Moslems and non-Moslems in Yugoslavia. Women who developed cervical cancer were more likely to manifest behavioral characteristics such as smoking, drinking of alcohol, and diminished religiosity. The cases were significantly shorter, lighter, and less endomorphic than controls similar in age, marital status, religion, and urban/rural residence. They also had somewhat higher systolic and diastolic blood pressures at two different readings. Multiple marriages and early initiation of coitus were more common among the cases. However, coital frequency was consistently lower among Moslem and non-Moslem cases than controls, both at the onset of coital practice and later. Absences from home and extramarital sexual experiences were significantly more common among the first husbands of the cases. An unexpected finding was the twofold or threefold greater mortality, especially at young ages, of first husbands of cases as compared with those of controls. The cases tended to experience more frequent and longer widowhoods beginning at earlier ages than controls. For most of the variables studied, case-control differences among the Moslem women closely resembled those among the non-Moslems. The results of this investigation are consistent with the venereal hypothesis of cervical carcinogenesis, but suggest the need for further investigations of the role of steroid hormones in this disease.

**17. CLINICOEPIDEMIOLOGIC STUDY OF UTERINE CANCER: COMPARATIVE ASPECTS OF THE ENDOMETRIAL AND CERVICAL SITES.**

Sharon Z, Shani M, Modan B
Dept. Clinical Epidemiology, Chaim Sheba Medical Center, Tel Hashomer, Israel
Obstet Gynecol; 50(5):536-540 1977

All newly diagnosed cases of cervical and endometrial carcinoma in Israel during the 5-yr period 1961-1965 were reviewed, and mean annual incidence rates of 4.9/100,000 and 7.4/100,000, respectively, were found. Cervical cancer was more prevalent in Moroccan-born women and among divorcees. The risk of endometrial cancer was highest for older, European-born, and single women, but it also appeared earlier in life. Postmenopausal bleeding was the most frequent first symptom at both sites. Fifty percent of the patients of both groups were diagnosed within 1 mo, but the delay was somewhat longer in the endometrial group. Median survival was 5 yr in patients with cervical cancer and greater than 12 yr in those with cancer of the corpus. The 5-yr survival was 50% and 75%, respectively. Survival tended to be better in younger patients in both groups. The gradual disappearance of intraethnic differences in Israel is expected to lead to a decrease in the incidence of invasive cervical cancer and an increased incidence of endometrial cancer. (16 Refs)

**18. MORTALITY FROM CANCER OF THE CERVIX IN LOUISIANA, 1960-1970.**

Newell GR, Stancliff EK
Sch. Pub. Hlth. Tropical Med., Tulane U., New Orleans, La.
J La State Med Soc; 124(8):280-286 1972

A study on cervical cancer mortality in Louisiana showed that the death rate for this condition in 1970 was 5.5/100,000 among white women and 15.4/100,000 among nonwhite women. Cervical cancer mortality among white women had declined steadily since 1960, but no improvement was seen in the death rate among nonwhite women. A steady increase in mortality in age groups 25-34 and 65 and over was seen. Cervical cancer mortality in Louisiana showed a good correlation with poverty indices including household without plumbing and female head of family. Among nonwhite women, there were fewer deaths among widows and more death among single women and divorcees than among white women.

**19. SYMPOSIUM ON PROSTATE CANCER.**

Cockett AT, Murphy GM, Bagshaw MA, Rhamy RK, Scardino PL
Div. Urology, Univ. Rochester Sch. Medicine Dentistry, Rochester, NY
Contemp Surg; 8(5):54-86 1976

Epidemiologic, diagnostic, and therapeutic aspects of prostatic carcinoma are discussed. Age-adjusted mortality figures range from 1/100,000/yr in China to 20/100,000 in South Africa. Mortality in the U.S among nonwhites is twice that of white men. Mortality is highest among divorced men and lowest among single men of all ages greater than 50 yr. No difference in 10-yr survivals was seen among pts who were given exogenous estrogens, those who were castrated, and those who were given estrogens following castration. The significance of positive nodes is discussed, and the importance of identification of high-risk groups is pointed out. For Stage C lesions, several approaches are possible: endocrine palliation, radical prostatectomy with seminal vesiculectomy, irradiation, and hormone therapy. Approx. 44% of pts have Stage C disease at diagnosis. Adrenalectomy and hypophysectomy are rarely recommended. Combined radiotherapy and prostatectomy have been used with success. Of pts treated with external beam radiation therapy alone, best results have been achieved in pts in whom disease was confined to the prostate. A 10% incidence of genitourinary sequellae may be anticipated after external beam radiotherapy, as well as a 10% incidence of gastrointestinal problems. Potency was maintained by 61% for at least 15 mo after treatment. A second definitive treatment of the tumor is possible with surgery in recurrence after irradiation. (no refs)

**20. SOME EPIDEMIOLOGICAL ASPECTS OF CANCER OF THE PROSTATE.**

King H, Diamond E, Lilienfeld AM
NCI, Bethesda
J Chronic Dis; 16(1):117-153 1963

In the hope of obtaining some indications as to the etiology of prostate carcinoma and some guidelines for future statistical research, the authors present an extensive review of the epidemiological literature in this field and an analysis of data from 33 cities in the USA regarding the trends in morbidity and mortality due to prostate cancer and the distribution by such characteristics as age, race, geographical area, nativity, religion, marital status, socioeconomic standing and familial aggregation. Some of the findings are: a continuing increase in mortality among the non-white population, an over-all mortality rate varying from 22.3/100,000 in the USA (non-white) to only 1.1/100,000 in Japan, a geometrical increase from the age of 40-50 upwards, a low frequency among Orientals and Indians but high among Negroes, a higher frequency in the northern USA than in the south, but little difference between urban and rural areas, a lower frequency among foreign-born whites than among native Americans, a low frequency among Jews and high frequency among Protestants, a higher frequency among married or divorced than among single persons, and a higher frequency among married with children, generally no socioeconomic gradient, but more frequent among

professionals than among workers, and a high frequency among male relatives of prostate cancer decedents. The authors conclude that both genetic and sociocultural factors (such as sexual behavior) probably play a role.

### 21. SOME EPIDEMIOLOGICAL FEATURES OF BREAST CANCER AMONG MALES.

Schottenfeld D, Lilienfeld AM
Dept. Chronic Dis., Johns Hopkins Sch. Hyg. Pub. Health, Baltimore, Md.
J Chronic Dis; 16(1):71-81 1963

The age specific mortality rates for male whites and non-whites with breast cancer in 1939-1941 and 1949-58 are presented, showing an exponential increase with age but a slight decrease for whites over the 20 yr period. Geographical variations in the incidence of breast cancer in the USA are also discussed, showing a lower incidence in the South, as well as some international comparisons which indicate very low rates in Finland and Japan. Other factors which should be considered are marital status and religion, since the mortality rates are particularly high in Jews and in divorced or widowed men of all religions.

## C. Cancer Occurrence in Relation to Behavioral and Cultural Values

### 22. SOCIAL TRAUMA IN THE EPIDEMIOLOGY OF CANCER OF THE CERVIX.

Graham S, Snell LM, Graham JB, Ford L
State U. New York, Buffalo, NY 14214
J Chronic Dis; 24(11):711-725 1971

Four hundred and forty-seven cases of cancer of the cervix were compared to 711 controls with other types of cancer and non-neoplastic diseases of other than genital organs from Roswell Park Memorial Institute. Cancer of the cervix cases were somewhat more likely to have been married two or more times, with 22.3 per cent having experienced at least two marriages as compared to 14.5 per cent of the controls. They were slightly more likely to have been married at a younger age. Thus, 26.1 per cent of the cases were married before the age of 19 as compared to 21.2 per cent for the controls. Only 3.1 per cent of the cases were first married over 30 yr of age as compared to 9.1 per cent of the controls. Cases of cancer of the cervix were of slightly lower socio-economic status and had had more pregnancies and live births than the controls. Further comparisons were made considering differences between cases and controls in age; size of family, including spouses, children, siblings, grandchildren, parents and other relatives; and whether the life events under consideration occurred among family members living in the subjects' or other households. Comparisons were made on the extent to which they and their family members had experienced death, divorce, illness, economic want, residential mobility, and feelings of being upset in the five yr prior to onset of the illness under consideration. The proportion of cases and controls experiencing various numbers of these incidents was also examined. No differences between cases and controls were found for any of these variables.

### 23. THE PSYCHOSOCIAL EPIDEMIOLOGY OF CANCER. (PP. 11-21)

Fox BH
Cancer, The Behavioral Dimensions. Cullen JW, Fox BH, Isom RN, ed. New York, Raven Press, 1976.

Social and personal characteristics and behavior as conditions associated with higher and lower risk of cancer and its consequences are discussed. Many of these conditions and behaviors and their range of confidence with respect to both increased or decreased risk for cancer are tabulated, along with the associated site. It is believed that schistosomiasis among Egyptian farm laborers produces a high risk of bladder cancer. The damming of the Nile, which caused an increase in schistosomiasis, may have increased the risk of bladder cancer. The relaxation of sexual mores may lead to an increased risk of cervical cancer, as early sexual experience and multiple partners can cause cervical erosion. This erosion is associated with greater risk of cancer. It is suggested that a public information program be undertaken to educate the public in the prevention of cancer and not just in its detection. A team including a psychosocial epidemiologist, economist, health systems planner, public health educator, medical education specialist, union health administrator, and relevant others should be formed. The purpose of this team would be to evaluate various behavior changes on the incidence and mortality associated with the various types of cancer and to study the possibilities of bringing about these behavior changes. (42 Refs)

### 24. RELATIONSHIP OF SOCIOCULTURAL FACTORS TO CANCER. (PP. 101-121)

Kegeles SS
Cancer, The Behavioral Dimensions. Cullen JW, Fox BH, Isom RN, ed. New York, Raven Press, 1976.

Subgroups of people more likely than others to be afflicted by or die from cancer and certain groups who do not take actions that will increase their chances of recovery from cancer were studied. Persons at risk for cancer are those with excess morbidity and mortality for certain sites of cancer and those who do not utilize preventive services. The various studies included a sociocultural study to determine causes of cancer and a study of sociocultural groups to determine reasons for low utilization of preventive services. Studies of subcultural group factors that may lead to poor health behavior included cognitive and attitudinal variables, subcultural definitional variables, life-style variables, and familial socialization variables. Health system factors that may limit participation, attitude change efforts, mass communication efforts, peer influence or diffusion strategies, and group discussion are discussed. (36 refs)

### 25. STUDIES IN THE EPIDEMIOLOGY OF PROSTATIC CANCER: EXPANDED SAMPLING.

Rotkin ID
Univ. Illinois Coll. Medicine, Chicago, IL 60612
Cancer Treat Rep; 61(2):173-180 1977

As a result of comparison of 111 prostatic cancer patients with matched control patients for selected risk variables, the patients are characterized by three main trends: delayed sexual drive and development, early repression of sexuality, and premature cessation of sexuality. Excessive numbers of patients reported occupational exposure to fertilizers and auto exhaust fumes. Diets of the patients were higher in animal fats. There were no differences between both groups in frequencies of multiple marriages or sex partners or stressful effects from selected events early or late in life. Trends for circumcision and other variables are presented. The data suggest that early differences are hormonally conditioned, they support a provisional endogenous rationale for initiation of prostatic cancer, and they oppose a hypothesis favoring transmissible oncogenic agents. If the results continue to hold up with increased sampling, limitation of sexual activity at any time of life may increase risk. (3 Refs)

## II. THE INCIDENCE OF CANCER IN PSYCHIATRIC PATIENTS

### 26. ON THE INCIDENCE OF MALIGNANCY AMONG SCHIZOPHRENIC PATIENTS.

Rassidakis NC, Kelepouris M, Goulis K, Karaiossefidis K
State Mental Hosp., Athens, Greece
Agressologie; 14(4):269-273 1973

Of the 2300 deaths occurring among patients in the State Mental Hospital of Athens between 1953 and 1971, 39 were due to malignant neoplasms. While only 14 of these deaths occurred among schizophrenics, the expected number of deaths among this group would be 38 (based on comparison with the mortality rate from cancer among the general population of Greece). In particular, the schizophrenic patients seemed to be protected against cancer of the digestive system. No substantial differences were found between the expected and actual number of deaths from cancer among the two other groups of patients dying from malignant neoplasms: alcoholics and drug addicts (7 patients), and those suffering from psychoses other than schizophrenia (18 patients).

### 27. THE INCIDENCE OF CANCER AMONG IN-PATIENTS WITH AFFECTIVE DISORDERS.

Evans NJ, Baldwin JA, Gath D
Radcliffe Infirmary, Oxford, England
Br J Psychiatry; 124:518-525 1974

Retrospective study of a group of 823 patients hospitalized for affective disorders sought to determine whether there was a statistically significant relationship between affective disorders and previously unsuspected carcinoma. A majority of patients (597) were diagnosed as reactive depressives according to ICD categories for affective disorders, although these diagnoses proved to be somewhat unstable over time. A total of 72 patients died from natural causes during the 4 yr follow-up period, with 4 patients dying of cancer diagnosed after the depressive illnesses. Deaths from all natural causes in the study cohort were significantly higher than expected for this age group, especially among women diagnosed as neurotic depressives (p less than .01). But cancer deaths in the studied cohort were not significantly higher than in the population at large. The hypothesis that depression might be an early indicator of latent carcinoma was thus not proved by the present study, which however confirmed earlier findings that deaths from all natural causes except cancer are higher in affective disorders than in the general population.

### 28. CANCER MORTALITY OF HOSPITALIZED PSYCHIATRIC PATIENTS.

Martin du Pan R, Muller C
Clinique psychiatrique universitaire, Hopital de Cery, CH-1008 Prilly/Lausanne, Switzerland
Schweiz Med Wochenschr; 107(17):597-604 1977

The literature on cancer mortality in hospitalized psychiatric patients, especially schizophrenics, is reviewed. Differences in the results and conclusions of these studies may be partially explained by the various statistical, sampling, and diagnostic methods and observation times that were used. There is some evidence that cancer mortality may be lower in schizophrenics, but this may be due to the lower exposure of hospitalized psychiatric patients to tobacco, alcohol, diet high in protein and fat, and sexual activity. It has been suggested that tranquilizing neuroleptics have an antimitotic action; on the other hand, reserpine and the rauwolfia alkaloids have been implicated in breast cancer. Other theories related to carcinogenesis, such as immunological deficit and the cancer personality, are discussed in relation to mental patients. A biochemical defect is thought by some investigators to be responsible for schizophrenia and, simultaneously, for diminished cancer risk. On the whole, however, it is concluded that there is no major difference between cancer incidence in a nonselected population of psychotic patients (excluding psychoorganic patients) and the general population. (73 Refs)

## III. PERSONALITY TRAITS ASSOCIATED WITH THE OCCURRENCE OF HUMAN CANCER

### A. Association Depression and Other Affective Disorders

### 29. EMOTIONAL AND PERSONALITY CHARACTERISTICS OF CANCER PATIENTS. (PP. 357-378)

Bahnson CB
Oncologic Medicine Clinical Topics and Practical Management. Sutnick AI, Engstrom PF, ed. Baltimore, University Park Press, 1976.

A review of the psychological and psychoanalytical literature revealed two main approaches to cancer: one related to loss and depression as an antecedent to cancer, and the other related to a particular personality configuration characterized by denial, repression, poor emotional outlet, and lack of self-communication. A recent study of patients with myocardial infarction, cancer (CA) patients, mixed sick controls, and normal controls involved the use of scales to measure anxiety, general proneness to suffer from minor somatic symptoms, stress, social commitment and conformity, and alienation. Age and socioeconomic status were also considered. The CA group rated lowest on all four anxiety scales and the somatization scale, but highest on that measuring perception of one's own physical health and resiliency. The CA group also rated lowest on recent stress and stress at work scales, but highest on that measuring childhood stress related to parental relationships. On scales reflecting feelings of being pushed or controlled by external demands and on the alientation scale, CA patients fell lowest; they scored high on social commitment and religiosity. Other studies are cited that related cancer to CNS changes, to transmittal from the CNS to target tissues, and to immunological responses as related to stress. Hormone studies showed both increased and decreased activities of various hormones associated with cancer; one demonstrated that every cancer type has its own profile of changes in hormone production, so that such a profile might serve as a predictor. These various psychological and immunological considerations show many conceptual similarities since both deal with relationships to self, with exhaustion and breakdown of defense systems, and with dual control systems governing each area. It is suggested that the next step in theoretical development will allow conception of the malignant process as a total life development. (91 refs)

### 30. PERSONALITY STRUCTURE OF BREAST CANCER PATIENTS (IV). DEPRESSION AND CANCER: A COMPARISON.

Lerer SB, Silva JL, Garcia D, Gomez R, Mendez JL
Departamento di Psiquiatria, Facultad de Medicina, Universidad Javeriana, Columbia
Univ Med (Bogota); 8(1):7-22 1976

Psychological studies were conducted compairing 20 breast cancer patients with 20 depressive neurotic women with hypochondriacal traits. All the women belonged to the same socio-economic class. In the cancer patients, there was a fantasy of a martyr mother and the shadowy remembrance and fantasy of an extremely poor early feeding. A more

massive phobic hysteric repression, as well as a lesser capacity to play, socialize and develop interpersonal relationships, was found in the patients with neoplasia. The adaptive reaction of adolescence was quiet in the cancer groups and their life pattern was passive; schooling and work were poorer and there was less assertiveness. Losses and their relationship to the triggering of symptoms were equivalent in both groups. A comparison is made between the hypochondriacal pride of the control and the minimization and submission found in the cancer patients. A comparison is also made of hypochondriacal depression and neurosis, and neoplastic somatization is compared with schizophrenic outbursts. It is believed there are contact points between the schizophrenic patient's acceptance of the psychotic role and the acceptance of defeat by the cancer patient. (21 Refs)

**31. PSYCHIATRY AND ONCOLOGY: A REVIEW.**

Brown JH, Varsamis J, Toews J, Shane M
Fac. Med., U. Manitoba, Winnipeg, Canada
Can Psychiatr Assoc J; 19(2):219-222 1974

There appears to be a definite and complex relationship between malignant disease and emotional disorders of an apparently endogenous kind, not related to gross brain damage, and antedating the discovery of the underlying malignancy. A disproportionately high number of patients treated for various affective disorders, notably depression, develop malignant disease shortly after receiving treatment; the death rate from carcinoma among these patients is significantly higher than predicted by national death rates. There may be an immunological relationship between malignant tissue and nervous tissue. Conversely, psychiatric disorders may be precursors of cancer. Cancer patients have special psychological characteristics which antedate the onset of cancer symptoms, and perhaps of cancer itself; these characteristics have to do with an inhibited life-style, loss of an important relationship, melancholy, and giving up. In addition, serum free fatty acids are raised in both depressive states and in cancer patients during periods of active tumor growth; insulin, tolbutamide, and reserpine, which lower serum free fatty acids, retard tumor growth. Psychiatric symptoms in patients with an established cancer include tension, depression, anxiety, aggressiveness, and paranoid attitudes. Patients with rapidly progressing cancer tend to evade and repress the anxiety-evoking reality of their illness more actively than those with relatively good prognoses. The former group also tends to cling less strongly to life, displays more depression, anxiety, and tension, be more passive and dependent, and be more aggressive than the latter group. It is suggested that an immunological mechanism may eventually explain the relationship of an underlying malignant disease to a psychiatric illness.

**32. PSYCHOSOMATIC ASPECTS OF CANCER.**

Fritzsche U
Arnikastrasse 2, D-8011 Vaterstetten, W. Germany
Med Klin ; 71(21):922-926 1976

Recent developments in the relation between carcinogenesis and the CNS are reviewed. The immunological system, whose competence is implicated in carcinogenesis, is under the same neuroregulatory constraints as any other system in the host. Beginning with the original correlation between involvement of the pallidum and corpus striatum in tumor proliferation, animal experiments are cited linking organ denervation and chronic CNS overstimulation with tumorigenesis. Psychoanalytic research has found correlations between premorbid conflict states, or persistent isolation, alienation, and sense of loss, mostly of pediatric origin, and higher tumor incidence. Various studies have correlated a high frequency of solid tumors and leukemias with "sadness" and "hopelessness" following the loss of a "key object".It is suggested that the presently increasing incidence of malignancy is a typical response to the extent of contemporary challenges. This is supported by the currently accepted immunological relation between embryonic and tumor tissue, a structural expression of "biological" regression coincident with the "psychic" regression of infantile behavior in cancer patients. It is concluded that the basis of the cancer problem is not cancer but the person with cancer. (37 refs)

**33. PSYCHOSOMATIC ASPECTS OF CANCER DISEASE. (PP. 46-66)**

Ringel E
Allgemeines Krankenhaus der Stadt Wien, A-1097 Vienna, Austria
Krebsbehandlung als Interdisziplinaere Aufgabe, Beitrage des Wiener Arbeitskreises feur Geschwulsthandlung. Karcher KH, ed. Berlin, Heidelberg, New York, Springer-Verlag, Springer-Verlag, 930 pp., 1975.

In this massive review the author marshalls evidence that emotive conflicts have physical correlates in bodily changes, including cancer. There are certain presuppositions. First, mental effects that are pathogenic occur via the emotions. Second, the crucial junction point between the mental and physical is the autonomic nervous system, with compensatory switching between sympathetic and parasympathetic fields; their balance can be disturbed by chronic trauma or stress. Third, psychosomatic disease occurs principally in systems under autonomic regulation, including the cardiovascular, respiratory, gastrointestinal, urogenital, endocrine, and skin tissue systems. Some of the psychic traumas correlated with tumorigenesis include loss of an essential personal relationship, withdrawal (regression) from unacceptable realities, inability to adapt to undesirable constraints (as smokers who will not dishabituate despite the threat of bronchial carcinoma), and intractable hopelessness. These correlates also exacerbate the course of cancer after onset, always unfavorably for the patient.

**34. PSYCHOLOGICAL FACTORS IN THE ETIOLOGY AND TREATMENT OF CANCER OF THE CERVIX.**

Labrum AH
Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY
Clin Obstet Gynecol; 19(2):419-430 1976

Squamous cell cancer of the cervix has been limited to women who are or have been sexually active. The two most important etiological factors in determining a predisposition for cervical cancer are age at first intercourse and the number of sexual partners. Many psychological studies of such patients have demonstrated a feeling of hopelessness in these women, defined as a feeling of despair or lack of purpose in life. Childhood and adolescent experiences in such patients have corresponded with indices of life-style 'conducive to cancer,' thus possibly leading to earlier and more frequent sexual intercourse as a pretext for being loved or needed. The woman with a more normal childhood and adolescence is only at risk for cervical cancer if she loses her partner, child, or purpose for living; however, she may have a better prognosis than the "hopeless" group. A discussion of the management of the terminal cancer patient is included.

**35. RAPIDLY PROGRESSIVE COURSE OF CANCER IN THE LIGHT OF THE PATIENTS' 'ANXIETY SCALE.'**

Herberger W
Hufeland Clin., Wittenberg, Germany
Z Psychosom Med Psychoanal; 9(4):271-285 1963

An intimate relationship was found to exist between the general psychological state of cancer patients and the rate of development of their disease. In 12/15 case histories reported in detail, rapid progression of the disease was linked at least partially to severe psychological trauma resulting in

depression and lack of desire to live; in 3/15, remarkable emotional stability and ability to cope with psychological stress were felt to be conducive to long survival. The patients included 12 females, ranging in age from 33 to 74 yr, and 3 males, 51-53 yr. The malignancies in the female patients included 8 mammary, 1 cervical, 1 ovarian and 1 pancreatic carcinoma, and 1 chronic myeloid leukemia; in the males there were 2 bronchial and 1 gastric carcinomas. Survival time ranged from 4 mo to 2.75 yr in the patients with depressive tendencies, but was 4 yr in the 3 patients able to compensate their psychological conflicts.

**36. ENVIRONMENTAL RISKS RELATED TO CANCER. (PP. 85-92)**

Peacock PB

Cancer, The Behavioral Dimensions. Cullen JW, Fox BH, Isom RN, ed. New York, Raven Press, 1976.

Environmental risks related to the incidence of cancer are discussed. Cigarette smokers are at a greatly increased risk of lung cancer as compared with nonsmokers. Lung cancer also shows an urban excess, particularly among men; however, this has not been definitely correlated with air pollution. Asbestos is highly carcinogenic for lung cancer. Compared with the risk of cigarette smoking, the effects of occupational exposures and air pollution are small. In experimental animals, an increased uptake of fat increases the yield of breast cancer; animals on a high fat diet are also more likely to get breast cancer when exposed to chemical carcinogens. There is a strong correlation between high fat diets and increased breast cancer in women. There is a similar correlation between cancer of the colon and fat intake; cancer of the kidney and possibly of the prostate may follow such a pattern. There is probably more than one carcinogenic pathway when dealing with cancer of the colon and fat. It has not yet been proved whether there is a correlation between a lack of dietary fiber and large bowel cancer. Cholestyramine, used to reduce serum cholesterol levels by increasing the fecal loss of bile acids, may increase the incidence of colon cancer. Consumption of large amounts of salty foods and small amounts of milk may be associated with carcinoma of the stomach. Aflatoxins from Aspergillus flavus are strongly associated with hepatic carcinoma. Nitrosamines in foodstuffs and halogenated hydrocarbons in drinking water may be carcinogenic. Estrogens, rauwolfia, alcohol, and reserpine-containing drugs may also be carcinogenic. Excess exposure to UV causes skin cancer. Psychological factors may also be associated with cancer, for example, persons with cancer of the pancreas show extreme states of depression. Priority attention should be given to modification of life-style habits that can be controlled: tobacco usage, incorrect nutrition, and alcohol usage. (49 Refs)

## B. Personality Traits Associated with the Occurrence of Human Cancer

**37. PSYCHOLOGICAL CORRELATES OF BREAST CANCER. (PP. 71-79)**

Greer HS

Risk Factors in Breast Cancer. Stoll BA, ed. Chicago, William Heinemann Medical Books Ltd, New Aspects of Breast Cancer, vol. 2, 1976.

A consecutive series of 160 women admitted to the hospital for breast tumor biopsy was studied psychologically by detailed structured interviews and standard tests. Interviews and testing were conducted on the day before operation, without knowledge of the provisional diagnosis. The information was verified by separate interviews with husbands or close relatives. Present results are based on statistical comparisons between 69 patients found to have breast cancer and a control group comprising the remaining 91 patients with benign breast disease. The principal finding was a significant association between the diagnosis of breast cancer and a behavior pattern, persisting throughout adult life, of abnormal release of emotion. This abnormality was extreme suppression of anger and, in patients over 40, extreme suppression of other feelings. Extreme expression of emotions, though much less common, also occurred in a higher proportion of cancer patients than controls. Previous reports of correlations between breast cancer on the one hand, and extraversion, previous emotional stress, and depressive states on the other, were not confirmed. (20 refs)

**38. THE RELATIONSHIP BETWEEN BREAST CANCER IN WOMEN AND THEIR LOCUS OF CONTROL AND HOSTILITY.**

Richards MC

Univ. Georgia, Athens, GA 30601

Diss Abstr Int B; 37(12,part1):6410 1977

The purpose of this investigation was to study the locus of control and the type and direction of hostility expressed by cancer and medical groups. Specifically, the study attempts to show whether one group of women with medically diagnosed carcinoma (cancer) is more hostile and externally oriented than a similar group of women with medical problems other than cancer (medical). The following hypothesis was tested: women with medically diagnosed cancer do not differ from women with other medical problems in the following characteristics: Locus of Control; Extrapunitiveness; Intropunitiveness; Impunitiveness; Obstacle dominance; Ego defense and Need criterion for rejection of the null hypothesis. Sixty females, 46 Caucasians and 14 blacks, between the ages of 50 and 65 served as subjects in the study. Thirty of these subjects were randomly selected from the breast cancer files of a Northeast Georgia hospital. The second group of 30 women are patients presently receiving treatment from the Northeast Georgia medical doctors for disease other than socioeconomic levels. There was an effort to insure a representative number from each socioeconomic level in each of the two groups. Two types of assessment instruments were used in this study: a test of hostility and a test of locus of control. The test of locus of control is Rotter's Internal-External Control of Reinforcement Scale. The test of hostility is Rosenzweig's Picture Frustration Study. Results of this study indicate that there is no significant difference between the cancer group on the dimension of extrapunitive, impunitive, obstacle dominance and ego defense of the Rosenzweig Picture Frustration Study. The study indicates that the women in the medical group tend to direct their hostility onto other persons and things and tend to let the obstacle in the frustrating situation dominate. (no Refs)

**39. WOMEN, CANCER AND EMOTIONS.**

Surawicz FG

Dept. Psychiatry, Univ. Kentucky Coll. Medicine, Lexington, KY 40507

J Am Med Wom Assoc; 32(1):18,20,26-27,29 1977

The association between mental illness and cancer of the cervix and cancer of the breast is discussed in terms of the following categories: the relationship between personality, psychodynamic conflict, or recent stress and the development of cancer; the role of cancer and its treatment in subsequent emotional problems; the personality of the patient and the course of the cancer; and personality factors and rehabilitation. Cancers of the female sexual organs were initially viewed as the somatic expression of unresolved psychosexual conflicts; currently, the view is more toward a somatopsychic disease. Successful treatment must center on the entire person and not just the lesion itself. A review of the historical literature is provided. (50 refs)

**40. PERSONALITY CHARACTERISTICS IN MALES CONDUCIVE TO LUNG CANCER.**

Kissen DM

Dept. Psycholog. Med., U. Glasgow, Scotland

Br J Med Psychol; 36(Pt1):27-36 1963

Among 161 male lung cancer patients interviewed or responding to a questionnaire (often before diagnosis of their disease had been made), fewer (26.1%) gave a history of childhood behavior disorders (e.g bedwetting, temper tantrums) than among 174 male non-cancer patients (41.4%). More of the cancer patients (59.7%) admitted to a tendency to conceal or bottle up emotional difficulties than controls (42.8%). There was no correlation with amount of cigarette smoking, nor with lack of aggression or sociability, nor with tumor histology. There was a marked statistical correlation, however, with a low mean score for neuroticism (previously reported). The patients tended to be somewhat extroverted.

**41. PERSONALITY CHARACTERISTICS OF WOMEN WITH GYNECOLOGICAL CANCER (MEETING ABSTRACT). (PP. 41-42)**

Mastrovito RC, Deguire K, Clarkin J, Lewis JL, Cooper E

Departments of Neurology, Gynecology and Social Work, Memorial Sloan-Kettering Cancer Center, New York City.

Third International Symposium On Detection And Prevention Of Cancer. 1976.

Recently several studies have been carried out exploring the psychosomatic aspects of cancer, ie the psychological factors in individuals which may be related to the etiology of their cancer. There are 2 major hypotheses which are the bases of these investigations: The so-called 'loss-depression theory' in which the onset of the cancer is related to significant life events, implying that the disease is likely to follow a significant object loss and lead to a sense of despair, hopelessness and depression; and the cancer-prone personality theory, which suggests that personal characteristics marked by the suppression of emotions make an individual more susceptible to the development of a malignancy. Our investigations have tested the latter hypothesis; that individuals who tend to be highly controlled, non-competitive, unassertive, inhibited, less energetic, spontaneous and independent will be found in significantly greater numbers in a cancer population than a non-cancer control group. Using the Adjective Check List, a psychological test which yields 24 personality scales, we studied 228 patients admitted to Memorial Hospital for the first time. The testing was limited to women admitted for suspected or confirmed gynecological malignancies and included patients with cancer of the ovary, uterus (including trophoblastic disease), cervix and vagina. Those patients for whom diagnostic work-up revealed no cancer comprised the control group. The Adjective Check List was administered shortly after admission to hospital and in most cases prior to a confirmed diagnosis. With few exceptions, the women in the non-cancer group were unaware that their disease was definitely benign. Of the 228 patients studied, 180 had a confirmed diagnosis of cancer, and 48 were discovered to have benign disease. When the experimental cancer group was compared to the non-cancer control group by an analysis of variance, results indicated that the women in the cancer group were more highly controlled, more conforming, less adventurous, assertive, autonomous, competitive and spontaneous than women in the control group. This personality configuration was drawn from 7 scales on the Adjective Check List which significantly differentiated between the 2 groups at p levels ranging from 0.001 to 0.023. The results were not affected by the ages of the women. (Author Abstract)

**42. A CLINICAL STUDY OF THE PSYCHOSOMATIC ASPECTS OF CANCER.**

Tenney VA

Asian Med J; 11(12):16-21 1968

A psychiatric study was made of 135 patients diagnosed as having cancer, and a specific personality pattern noted. The patients seemed to have a secret self-loathing, which was masked, even to themselves, by a self-image supported by an emotional relationship with another person or by a respected position in society. When this image was destroyed, either by removal of the person through which he expressed himself, or loss of his position, this self-hatred became manifest and the patient did not consider himself anything worth living for. This may, possibly through hormonal mechanisms, accelerate the progress of cancer to a fatal end. Several case histories are presented.

**43. PSYCHO-SOCIOLOGICAL AND ANTHROPOLOGICAL ANALYSIS OF LEUKEMIC PATIENTS.**

Aleksandrowicz J, Brozek A, Kaczanowski K, Kepinski A, Zurowska A

3rd Clin. Intern., Acad. Med. Cracow, Poland

Sangre (Barc); 9(1):5-8 1964

In regards to 100 patients with different types of leukemia, a discussion is presented of such factors as psychosocial, financial and educational conditions; family conditions as children and as adults, presence of periods of conflict, personality expressed as 'moods,' personality in relation to other people in the environment, family and work conflicts and the results of Rorschach tests. According to the Kretchmer constitutional classification, of 49 women and 58 men with leukemia, pyknic and athletic types comprised the majority of lymphatic leukemia patients; the majority of chronic granulocytic leukemia patients were leptosomic. There were striking physiognomic similarities in the faces of each group of leukemic patients The psychosomatic correlation with different types of leukemia creates an impression that, depending on the psychosomatic type, the unknown leukemogenic factors initiate a proliferative reaction of either the lymphoreticular or the granulocytic tissue.

**44. THE PSYCHOSOMATICS OF BREAST CARCINOMA.**

Beck D, Konig U, Blaser P, Meyer R, Styk J, Ryhiner O

Kantonsspital Basel, Hebelstrasse 1, CH-4056, Basel, Switzerland

Z Psychosom Med Psychoanal; 21(2):101-117 1975

The comparative personality profiles of 50 women, 25 each with breast carcinoma (BC) and cystic mastopathy (CM), are examined. All BC had been mastectomized after histological confirmation of adeno-, scirrhous, or simple carcinoma. The mean ages of BC and CM were 42 and 33 yr, respectively, with a 19- to 50-yr range. One BC and 6 CM were single, 22 BC and 16 CM were married, 10 BC and 3 CM were separated, and 2 BC and no CM were widowed. One BC and 6 CM had full-time occupations, 9 BC and 5 CM were both employed and housewives, and 15 BC and 13 CM were housewives only. Seven CM and 12 BC came from broken homes (11 BC after age 5); the sibship configuration was about equal. Among the BC there had been a strong pediatric psychological ambience of family, particularly maternal idealization. The paternal relationship was predominantly remembered as benign. The CM group had mainly unfavorable family recollections, which were especially aggressive against the father. Fewer BC felt alone or unwanted as children and far fewer had fantasies about loss. The BC group was less realistic, had more defense mechanisms, and tended to suppress evidence of conflict.

In personality profile studies (interview and Minnesota Multiphasic Personality Inventory test), the BC group registered significantly higher hysterical and hypochondriacal levels and significantly lower aggressive levels than CM. The idealized maternal relationship was inferentially crucial to the BC group, since in reality half the group had lost a mother or stepmother 3 yr prior to discovery of the cancer; only three CM had similar losses. One-half of the CM group, but only one-quarter of the BC, were psychologically disturbed about chronic, routine stress situations (marriage, money, etc.). In 8 BC and 10 CM no relation between disease and psychological deficit could be identified. Given the complete sense of helplessness among BC after the loss of maternal security, breast cancer and subsequent mastectomy are seen symbolically as a physical re-enactment of the psychological separation.

## C. Psychological Testing in the Prediction of Human Cancer Risk

### 45. DEVELOPMENT OF A PSYCHOSOCIAL SCREENING QUESTIONNAIRE FOR CANCER (MEETING ABSTRACT). (PP. 42)

Bahnson MB, Bahnson CB
Eastern Pennsylvania Psychiatric Inst. Philadelphia, Pennsylvania, USA
Third International Symposium On Detection And Prevention Of Cancer. 1976.

Based on several studies by this group and other investigators, a screening questionnaire for cancer has been constructed utilizing items related to psychosocial variables and personal history. Questionnaire items cover the topics of 1) loss and reactions to loss of close relatives by death, 2) stress and recent life changes, 3) denial of interpersonal conflict, 4) childhood familial attitudes and relationships, 5) awareness and expression of affect: childhood and adult, 6) presentation of socially desirable attitudes, 7) locus of control (internal vs external), 8) living habits. Application of multivariate analysis techniques to data acquired from objectively interviewed subjects permitted discrimination between cancer patients and both normal and sick controls at statistically significant levels (.05 to beyond .001). This questionnaire, in German translation, has very recently been run on a West German sample of both male and female cancer patients and normal controls. Analyses to date support cross-validation at a statistically significant level. This questionnaire is now part of a longitudinal screening program scheduled to screen several thousand persons (age 40-65) yearly in a high cancer incidence section of the US. Utilization of the questionnaire in this project will provide evaluation of the 5%-30% improvement in identification of persons at risk for cancer projected on the basis of the experimental program described herein. (Author Abstract)

### 46. IS CANCER ALSO A PSYCHOSOCIAL PROBLEM?

Cramer I, Blohmke M, Scherg H
Lehrstuhl fur Arbeits- und Sozialmedizin, Abt. fur Sozialmed. Epidemiologie und Arbeitsphysiologie der Univ., Im Neuenheimer Feld 326, 69 Heidelberg, W. Germany
Fortschr Med; 95(27):1709-1710 1977

With the aid of a standardized psychosocial questionnaire and clinical investigation, it may be possible to organize a risk-profile that enables a better classification of a high risk patient population. This would provide an aid in diagnosis, prognosis, therapy and rehabilitation. Using the Bahnson modified questionnaire, 40 women (30 with mammary carcinomas, 4 with lung carcinomas, 6 with stomach carcinomas) between the ages 36-64 yr were compared to another 40 women (matched pairs) of the control group. Significant differences between cancer patients and the control group were seen in answers pertaining to religion, normal social obligations, social standing, recognition of authority, sensitivity, estimations of one's body strength and external control. Cancer patients gave more positive answers to these questions than the control group. Patients developing carcinomas showed certain personality traits: longer lasting phases of fear, sorrow and chronic stress. Next to genetic factors, childhood experiences and influences play an important role in differentiating the risk-type patient. (no Refs)

### 47. PSYCHOSOCIAL FACTORS AND CANCER. A STUDY OF 80 WOMEN BY MEANS OF A PSYCHOSOCIAL QUESTIONNAIRE.

Cramer I, Blohmke M, Bahnson CB, Bahnson MB, Scherg H, Weinhold M
Abteilung fur sozialmedizinische, Lehrstuhl fur Arbeits- und Sozialmedizin der Universitat, Im Neuenheimer Feld, D-6900 Heidelberg 1, W. Germany
Munch Med Wochenschr; 119(43):1387-1392 1977

Results of a questionnaire to study psychosocial factors and cancer in 40 women (aged 36-64 yr) with cancer (30 breast, 6 gastric, 4 pulmonary carcinomas) and 40 control women selected by the matched pairs method are presented. Cross-section examination of the women by questionnaire showed significant differences (p less than or equal to 0.05) between cancer patients and control subjects in 10 individual variables including health during the last 3 yr, attitudes, childhood neuroses, and the reactions during anger. Women with cancer experienced greater pressure during World War II bombings than patients without cancer. Discriminant analysis (by multivariant examination) revealed a discriminant function of 12 variables which permitted classification of women into carcinoma and control groups with 95% accuracy, and allowed for the classification of future cases into these two groups. A certain personality type with a higher frequency of developing carcinomas is established. (15 Refs)

### 48. STUDY OF THE PERSONALITY CHARACTERISTICS OF LUNG-CANCER PATIENTS.

Levendel L, Mezei A, Erdely E, Litvai G
Orszagos Koranyi Tbc es Pulmonologiai Intezet, H-1529 Budapest, 124, Hungary
Z Psychosom Med Psychoanal; 21(3):270-283 1975

The experimental design attempts to discover whether psychological tests, especially Rorschach, can harvest personality traits contributory to early diagnosis in suspected cancer patients. The personality studies involved in the tests are also examined for potential in measuring psychological effects on disease patterns, given the high incidence of incurable lung cancer and its emotive concomitants. The experimental groups consisted of 125 histologically confirmed malignancies (A), 25 suspected lung cancer patients (B), and 50 patients in different stages of pulmonary tuberculosis; the control group included 50 healthy persons. The M:F sex ratio was 7:3; 75% were over 45 yr of age. Based on 26 criteria, representing various responses to questions, personality profiles could be drawn. The cancer patients could be significantly differentiated from the other samples in 17 of the criteria, particularly those clustering around a sense of impending crisis ('catastrophe syndrome'). (13 refs)

### 49. STUDIES ON THE PSYCHOSOMATIC ASPECT OF MALIGNANT TUMORS WITH THE AID OF RORSCHACH TESTS.

Mezei A, Nemeth G
77 Amerikai St., Budapest, Hungary
Z Psychosom Med Psychoanal; 9(4):265-270 1963

Rorschach tests were given to 50 cancer patients (15 males, 35 females); 25 patients with nonmalignant tumors were used as controls. The responses showed significant differences between the cancer patients and the control group.

Outstanding characteristics of the former were (1) extreme insecurity, manifested by severe self-criticism and doubt (34/50); (2) disintegration of the 'body concept,' as evidenced by failure to come up with valid 'anatomy responses' (17/50); (3) loss of the functions normally used for interpretation, as shown by the patients' tendency to ask the investigator for help (8/50); and (4) increased awareness of 'threatening' symbols (11/50). It is believed that cancer disease is associated with specific personality traits, which can be determined by means of Rorschach tests.

**50. PSYCHE - NERVOUS SYSTEM - NEOPLASTIC PROCESS: AN OLD PROBLEM WITH NEW INTEREST. PART III: CLINICAL OBSERVATIONS AND INVESTIGATION ON PSYCHOSOMATICS OF CANCER, PARTICULARLY BY THE PSYCHOANALYTICAL OR PSYCHOSOMATIC METHOD.**

Baltrusch HJ, Austarheim K, Baltrusch E
19 Babenend St., Oldenburg 29, Oldenburg, Germany
Z Psychosom Med Psychoanal; 10(3):157-169 1964

This is a review on the role of personality and psychological and psychosomatic factors in the initiation and the course of neoplastic diseases. There seems to be a high degree of agreement in literature on the 'cancer-prone' personality type. Comparisons of Rorschach findings by 7 independent authors are tabulated.

**51. CANCER LINKED TO PERSONALITY TRAITS.**

Anonymous
No affiliation given
Med World News; 17(12):17-18 1976

The author presents data to suggest that a significant positive correlation exists between carcinogenesis and personality. The hypothesis is that women who either abnormally suppress or express their emotions have a higher risk of cancer than women whose emotional responses are more moderate. Psychological testing can have a greater than 80% accuracy in predicting cancers in various types of patients. This procedure could be important, as a mass screening program, in identifying high risk cancer subjects in the general population.

**52. THE SELECTION OF PATIENTS FOR BREAST CANCER SCREENING - IS THERE A ROLE FOR PSYCHOLOGICAL TESTING?**

Simpson JS, Morris T, Pettingale KW, Greer HS, Ryan K
Faith Courtauld Unit Human Res. in Cancer, King's Coll. Hosp. Medical Sch., London, S.E.5, England
Clin Oncol; 2(4):323-326 1976

A study was conducted of 146 women to see if there is a role for psychological testing in the screening of patients for breast cancer. It appears that psychological variables which distinguish the patient groups are constant throughout adult life. Thus, it might be possible to define a group of women who have an increased risk of developing breast cancer by a single psychological assessment given at any age. (8 refs)

**53. GEOGRAPHIC ONCOLOGY AND EPIDEMIOLOGY. ENVIRONMENTAL ONCOLOGY OF PHYSICAL AND CHEMICAL CARCINOGENS IN GLOBAL ONCOLOGY.**

Mosinger M
Institut de Synthese et Prospective de Recherche biomedicale et biophysique et d'expertise scientifique, Marseille, France
Med Biol Environ; 4(1):4-5 1976

Epidemiological research on cancer can produce valuable data, such as the studies on Burkitt's lymphoma, when the methodology is appropriate and the geographical region is chosen carefully. In most cancers, exogenous and endogenous factors interact in a complex manner, and a system is proposed for defining some of these factors in epidemiological studies. (1) For any geographic area, a profile of the environment should be obtained by measuring the physical, chemical, macrobiotic, microbiological, viral, and psychosociological parameters of the area. (2) In addition, data should be gathered on the inhabitants of the geographical area, including heredity, clinical family history, histology, physiology, and psychology and the bacteria and viruses that they might carry. Such a profile would be called a biogram. Statistical analysis of these data could lead to important fundamental information on human carcinogenesis. (no Refs)

**54. PROBLEMS, TASKS AND LIMITS OF PSYCHOSOMATIC CANCER RESEARCH.**

Baltrusch HJ
19 Babenend St, Oldenberg 29, Oldenberg, West Germany
Z Psychosom Med Psychoanal; 9(4):285-294 1963

The problems and tasks confronting psychosomatic cancer research are seen to fall into three major categories including (1) psychological studies; (2) psychophysiological investigations in cancer patients; and (3) psychosomatic animal experiments. Under (1), some specific problems mentioned are: effect of personality patterns on the development of the disease and its progress; definition of a 'cancer prone personality'; affinity of certain types of malignancies to different psychodynamic personality types; evaluation of psychological states such as despair, depression, etc, as contributing factors; incidence of cancer in persons with abnormal or psychotic behavior patterns (criminals, prostitutes, mental patients, etc); group investigations on a transcultural basis in various countries, civilizations, races and societies; investigation of the everyday habits of cancer patients, especially with regard to eating, smoking, and drinking habits; and comparison of different age groups characterized by a high incidence of cancer, such as childhood and old age. Under (2), the author lists studies on nervous functions, hormonal balance, immunological reactions; the role of chronic inflammations and trauma; and analysis of the previous history of the cancer patient with respect to psychosomatic background data. Under (3), it is advocated that psychosomatic animal experiments be conducted in species 'sociologically close' to man, such as the domestic dog.

## IV. ENDOCRINOLOGICAL AND IMMUNOLOGICAL CORRELATES OF PSYCHOLOGICAL FACTORS AND CANCER

**55. THE ROLE OF STRESS IN MALIGNANCY (MEETING ABSTRACT). (PP. 39)**

Riley V, Spackman D, McClanahan H, Santisteban GA
Pacific Northwest Research Foundation, and Fred Hutchinson Cancer Research Center, Seattle, Wa. 98104, USA.
Third International Symposium On Detection And Prevention Of Cancer. 1976.

Emotional or psychosocial stress produces increased levels of adrenal corticoids, and other hormones, through well-known neuroendocrine pathways involving the cerebral cortex, the hypothalamus, the pituitary, and the adrenal cortex. A direct consequence of the resulting plasma corticoid

elevation is injury to important elements of the immunological apparatus, which may leave the subject vulnerable to the action of latent oncogenic viruses, newly transformed cancer cells, or other incipient pathological processes that are normally held in check by an intact immunological apparatus, or other defensive surveillance system. The physiological and biochemical details of these processes are being studied in our laboratories using rodent models, with the expectation that biological principles which apply to mice may be relevant in some respects to humans. Our attention is thus directed to an examination of the adverse influences that elevated concentrations of circulating adrenal corticoids have upon the thymus and thymus-dependent T cells, inasmuch as these elements constitute a major defense system against various neoplastic processes, including those involving viruses and transformed malignant cells.

In order to establish the potential pathological influence of alterations in adrenal corticoid levels, we have compared the biochemical and cellular effects resulting from emotional stress with those which occur following imitation of 'stress' through the direct administration of natural or synthetic corticoids. We have found that both naturally occurring and chemically induced 'stress' produce similar biological effects in mice. In both cases, there is a decrease in the weight of various immunological organs including the thymus, spleen, and peripheral lymph nodes, as well as a lymphocytopenia. When the natural process was exaggerated by administering higher doses of synthetic corticoids, significant changes were also observed in other organs. A single dose of 50 mg/kg of dexamethasone, for example, induced all of the qualitative changes observed following emotional stress, and in addition, caused alterations in the weights of the ovaries, liver, and adrenals. It is concluded that emotional or psychosocial stress can be quantitatively measured by both biochemical and cellular parameters, providing that a truly quiescent baseline of these conditions can be obtained in the experimental animals by the use of protective housing. Typical environmental-related stress can be partially simulated by the direct administration of natural or synthetic hormones, which permit the resulting physiological alterations to be employed in controlled studies designed to examine the effects of stress on either the incidence or the course of neoplastic and other pathological processes. (Author Abstract)

## 56. PSYCHOENDOCRINE ASPECTS OF CANCER OF THE BREAST.

Katz JL, Ackman P, Rothwax Y, Sachar EJ, Weiner H, Hellman L, Gallagher TF
Montefiore Hosp. Med. Ctr., Bronx, N. Y.
Psychosom Med; 32(1):1-18 1970

Psychiatric interviews were made on 30 women (6 Negro, 2 Puerto Rican and the rest white) prior to biopsy of a breast tumor in order to assess their ego defenses and correlate them with daily hydrocortisone production, urinary hydrocortisone and androgen metabolites. The rank order correlation between the scores for extent of defensive failing and production of hydrocortisone was 0.48 (p below 0.02) and for excretion of metabolites (tetrahydrocortisone, tetrahydrocortisol, and allotetrahydrocortisol) 0.38 (p below 0.05). Considering only the 22 women whose tumors were malignant, the correlation was 0.50 (p below 0.02) and 0.49 (p below 0.02), resp. Scores from a single interviewer were more accurate than inter-rater analysis of the taped interview, and affect was the best 'predictor' of hydrocortisone production rate. There was no correlation with androgen metabolites.

## 57. SERUM IGA AND EMOTIONAL EXPRESSION IN BREAST CANCER PATIENTS.

Pettingale KW, Greer S, Tee DE
Faith Courtauld Unit, King's Coll. Hosp. Medical Sch., Denmark Hill, London S.E.5., England
J Psychosom Res; 21(5):395-399 1977

Serum immunoglobulins and expression of anger were measured preoperatively in 160 women admitted consecutively for breast tumor biopsy between 1971 and 1973. All women were less than 70 yr of age and had masses less than 5 cm in diameter. Serum IgA was significantly higher (p less than 0.001) in patients with extreme suppression of anger. Other serum immunoglobulin levels did not differ significantly, and they were not related to any expression of emotion other than anger. Postoperatively, the 69 women with breast cancer and 91 women with benign disease were separated into diagnostic groups, and serum IgA was measured at 3 mo, 1 yr, and 2 yr. At each follow-up in both groups of patients, serum IgA levels were higher in patients with extreme suppresion of anger. In the benign breast disease patients, these levels were only significantly higher preoperatively. In the breast cancer patients, significant differences were noted preoperatively and at 3 mo and 2 yr postoperatively. There may be a psychobiological link in the pathogenesis of breast cancer. (20 Refs)

## 58. INFANTILE STRESS, IMMUNE MODULATION, AND DISEASE PATTERNS.

Dutz W, Kohout E, Rossipal E, Vessal K
No affiliation given
Pathol Annu; 11:415-454 1976

Evidence for the concept of persistent immune modulation and its contribution to disease prevalence is reviewed. Also, results from a study on infants with various nutritious and infectious disorders from an Iranian orphanage are reported. Low immunoglobulin (Ig)G and high IgM serum levels were characteristic for infected, malnourished and/or premature infants. Numerous studies have shown that malnutrition and stress in early life interfere with cell-mediated (T-cell) immunity. A model is proposed for a relationship between T-cell levels and the onset of neoplasia; the incidence of neoplasia along with atrophy of the cell-mediated immune system increases with age. Although this immunity plays only a small role in prevention of chemical carcinogenesis, it seems to be of great importance in the development of lymphoma and neoplasia of the upper gastrointestinal tract. Studies of the frequency and geographic prevalence of lymphomas are described. Early infantile infection appears to lead to thymic atrophy and T-cell deficiency, hyperplasia of the B-cell system due to B-cell stimulation and finally the development of a B-cell lymphoma targeted to nasopharyngeal, cervical and abdominal lymph nodes. Immune inbalance in both ulcerative colitis and Crohn's disease appears to favor the development of neoplasia. (252 Refs)

## 59. MUTATION-METABOLIC MODEL OF CANCER DEVELOPMENT AND TUMOR PROGRESSION.

Dil'man VM
Laboratory of Endocrinology, N. N. Petrov Research Institute of Oncology USSR Ministry of Health, Leningrad
Vopr Onkol; 22(8):3-16 1976

The given data indicate the presence of a negative correlation between metabolic indices (a decrease of the tolerance to glucose, increase of the blood level of free fatty acids, insulin, cholesterol, triglycerides, cortisol, etc) and the indices of cellular immunity, which is determined by the number of rosette-forming cells and blastotransformation reaction to PHA and skin tests. Accordingly, the administration of an antidiabetic drug-phenformin

(phenetylbiguanide)-apart from the improvement of metabolic pattern, results in the restoration of the cell-mediated immunity indices. These findings provide a basis for stating the phenomenon of metabolic immunodepression. The metabolic immunodepression may prevent immunological surveillance activation, which normally is realized through the signals, provided by cells subjected to somatic mutation. It is noteworthy that the given metabolic conditions (hypercholesterinemia, hyperinsulinemia, the enhanced utilization of free fatty acids) promote the division of somatic cells. Thus, the same metabolic shifts which increase the pull of proliferating cells and, accordingly, increase the possibility of mutation development, also cause the metabolic immunodepression at the same time. These opposite metabolic influences on somatic cells and T-dependent lymphocytes cause the development of the syndrome of cancerophilia. The syndrome of cancerophilia normally arises at pregnancy, in intensive growth of the organism in childhood, accelerated development, stress and during normal ageing. Many carcinogens cause the decrease of tolerance to glucose, the increase in blood-insulin level and elevation of the threshold of sensitivity of the hypothalamus to feedback suppression. This phenomenon is based on the decrease of catecholamine level in the hypothalamus in ageing, stress and the action of some carcinogens. Thus, the syndrome of cancerophilia provides the conditions for cancer development and tumor progression and the tumor itself produces the metabolic shifts typical of cancerophilia. In the light of mutation-metabolic model of cancer development, it is possible to consider the fundamental factors which increase or hinder carcinogenesis. (Author Abstract)

**60. METABOLIC IMMUNODEPRESSION WHICH INCREASES THE RISK OF CANCER.**

Dilman VM

Prof. N. N. Petrov Res. Inst. Oncology, Leningrad, USSR

Lancet; 2(8050):1207-1209 1977

Metabolic changes that result in increased blood levels of free fatty acids (FFA), insulin, cholesterol, or triglycerides are followed by a decrease in cellular immunity. These metabolic changes also promote the division of somatic, nonlymphoid cells, a combination of effects that encourages carcinogenesis. The activity of any function controlled by the hypothalamic feedback mechanism may be intensified if the hypothalamic threshold of sensitivity to homostatic stimuli is raised. This occurs in aging and accounts for the fact that similar hormonal-metabolic patterns are observed in stress, normal aging, and pregnancy. Many chemical carcinogens raise the hypothalamic threshold to feedback control mechanisms, decrease glucose tolerance, and increase blood insulin, changes associated with cancer proneness. It is concluded that cancer proneness develops whenever there is a shift toward the predominant utilization of FFA. This occurs with pregnancy, rapid growth, stress, normal aging, obesity, adult-onset diabetes, and exposure to some chemical carcinogens. (56 Refs)

**61. METABOLIC PARAMETERS IN WOMEN WITH METASTATIC BREAST CANCER.**

Carter AC, Lefkon BW, Farlin M, Feldman EB

Dep. Med., State Univ. New York, Brooklyn

J Clin Endocrinol Metab; 40(2):260-264 1975

Data of glucose tolerance, hormone secretion, and metabolic response to growth hormone in groups of 6-11 breast cancer patients and healthy women are compared. Baseline metabolic and hormone secretion data acquired from a large number of breast cancer patients are presented. Mean glucose tolerance was impaired in women with breast cancer. Mean plasma glucose at 1 hr was significantly greater than in healthy subjects. Insulin secretion was delayed and prolonged in cancer patients. Mean baseline level of growth hormone in cancer patients (1.8 plus or minus 0.62 ng/ml) was significantly greater than mean growth hormone (0.74 plus or minus 0.23 ng/ml) in healthy subjects. In cancer patients and control subjects given saline, free fatty acids (FFA) increased similarly. After injection of human growth hormone, FFA levels were not significantly changed in cancer patients but were much greater in the controls. Cortisol and protein-bound iodine levels were normal and there was no lipolytic factor in the sera of breast cancer patients. The changes in breast cancer patients were not attributable to age, obesity, inanition, or stress. It is suggested that the incidence of breast cancer may be increased in patients with such metabolic defects, or the tumor may adversely affect the tissue metabolism of the host.

**62. THE METABOLISM OF STEROID HORMONES IN BREAST CANCER: A REAPPRAISAL. (PP. 36-50)**

Brooks SC

Steroid Hormone Action and Cancer. Menon KM, Reel JR, ed. New York, Plenum Press, Current Topics in Molecular Endocrinology, vol. 4, 1976.

The metabolism of steroid hormones in breast cancer is reappraised. The relationship between urinary steroid patterns and breast cancer is attributed to variations in the metabolism of hepatic steroids; the variants are representative of the microbial oxidase systems; their inducibility has been observed in rodents to be genetically determined. The activity of the hepatic oxidases can be stimulated by the corticosteroids resulting from stress; the inducers have been demonstrated to include environmental carcinogens as well as drugs. It is concluded that the differences in steroid hormone metabolism may be related to an alteration of the body's functions that results in breast cancer, or to a process directly responsible for carcinogenesis in the breast. (89 refs)

**63. PSYCHOPHYSIOLOGIC ASPECTS OF CANCER: THE JAMES EWING LECTURE.**

Miller TR

1275 York Avenue, New York, NY 10021.

Cancer; 39(2):413-418 1977

Clinicians have long been aware of the influence of the neuro-endocrine axis and the action of the hypothalmus on the humoral immune response in the origin and course of cancer. Little attention has been paid, however, to the psychophysiologic aspects of cancer. These psycho-social effects may be related to hypothalamic activity, the autonomic nervous system, and neuro-endocrine activity. More attention should be paid to the manipulation of the psyche in the prevention and management of cancer. (14 Refs) (Author Abstract)

**64. PSYCHE - NERVOUS SYSTEM - NEOPLASTIC PROCESS: AN OLD PROBLEM WITH NEW INTEREST. PART II: NEURAL RELATIONS.**

Baltrusch HJ

19 Babenend St, Oldenberg 29, Oldenberg, West Germany

Z Psychosom Med Psychoanal; 10(1):1-10 1964

This paper is a review of the etiologic role of the nervous and hormonal systems and of various biologic secretions and products in neoplastic diseases.

**65. ALCOHOL AND CANCER.**

Zanoboni A, Zanoboni-Muciaccia W

Istituto di Clinica Medica IV, Universita di Milano, 20122 Milan, Italy

Lancet; 1(7974):1408 1976

An enhanced pituitary prolactin reserve was observed after a thyrotropin-releasing hormone stimulation test in alcoholic cirrhotic male patients. The basal values were only slightly raised, and plasma-prolactin concentrations were significantly higher than in normal controls. These data supp-

ort the hypothesis that alcohol stimulates the anterior pituitary secretion of the three tropic hormones. The authors also demonstrate a link between alcohol or psychotropic drugs and prolactin release. It is thought that these effects may explain the association between alcohol ingestion and higher incidences of cancers. (8 refs)

**66. LOW BLOOD PRESSURE AND CANCER.**

Pellanda EB

Sao Pedro Hosp., Porto Alegre, Brazil

Folha Med; 48(5):243-261 1964

Anamnesis of 315 patients of both sexes with various malignancies showed relatively low blood pressure as compared with normal av from the literature. There seems to be some evidence that hypertensive individuals are relatively resistant to neoplastic processes. Hormonal predisposition for cancer, particularly when there is a shortage of mineralocorticoids in relation to other hormones, was discussed and reviewed. A psycho-endocrine relationship to cancer was mentioned.

# V. EXPERIMENTAL STUDIES ON THE PHYSIOLOGICAL EFFECTS OF STRESS IN RELATION TO CANCER INDUCTION

## A. Hormonal and Immunological Effects of Environmental Stress in Animals

**67. THE EFFECT OF STRESS ON SERUM PROLACTIN IN THE FEMALE RAT.**

Riegle GD, Meites J

Dept. Physiology, Michigan State Univ., East Lansing, MI 48824

Proc Soc Exp Biol Med; 152(3):441-448 1976

To determine the effect of stressors of varying intensities on prolactin secretion in female Long-Evans rats in a variety of physiological states, changes in serum prolactin in response to ether vapor, ether vapor plus serial bleeding, acute restraint and chronic restraint stresses were measured in cycling, castrate, pregnant, and lactating rats. Serum prolactin was measured by radioimmunoassays in serial blood samples taken before and after administration of each stressor. Pretreatment prolactin levels were elevated in rats in the afternoon of proestrus and estrus, on day 1 of pregnancy, and during lactation. Low initial prolactin concentrations were observed during diestrus, on the morning of estrus, and in castrate females. Low intensity stress, such as ether vapor alone, did not affect serum prolactin concentrations in any group. The effect of higher intensity stress was related to the pretreatment concentration of serum prolactin. If the initial prolactin levels were high, as on the afternoon of proestrus and estrus, on day 1 of pregnancy, and during lactation, high intensity stress was associated with a reduction in serum prolactin in all cases except for the group of rats which on the afternoon of estrus received the restraint stress treatment. If the pretreatment prolactin levels were low, as in diestrous and castrate rats, high intensity stress increased serum prolactin concentrations. Rats subjected to chronic restraint stress had increased pretreatment serum prolactin during the treatment regime. Although their initial prolactin concentrations were increased, these rats had lowered levels of prolactin at the end of their restraint periods. These data reaffirm the importance of understanding the effects of stress on hormone control mechanisms, and emphasize the importance of avoiding irregular or undue stress in animals used for studies of prolactin secretion.

**68. INFLUENCE OF RESTRAINT ON PLASMA PROLACTIN AND CORTICOSTERONE IN FEMALE RATS.**

Smith SW, Gala RR

Dept. Physiology, Wayne State Univ. Sch. Medicine, 540 E. Canfield, Detroit, MI 48201

J Endocrinol; 74(2):303-314 1977

The influence of restraint as a form of acute stress on plasma prolactin and corticosterone concentration was investigated in ovariectomized (OVX) and OVX, estrogenized (OVX-PEP) female Sprague-Dawley rats. Plasma concentrations were monitored by way of a catheter inserted into the left carotid artery. The animals were removed from their cages, had their hind legs secured with a paper covered wire and were returned to their cages. The prolactin levels in OVX animals were not significantly altered when restraint was applied either in the morning or in the afternoon. In the OVX-PEP rats plasma prolactin was significantly increased by restraint during the morning. Restraint of these animals in the afternoon caused either a delayed suppression of the raised levels, or induced an increase depending on whether or not the afternoon surge had started. Corticosterone values increased under restraint in both OVX-PEP and PVX animal in the morning and afternoon. In adrenalectomized (ADX) OVX-PEP animals, restraint resulted in only a slight increase 15 min after initiation of restraint. OVX-PEP animals maintained on 0.9% NaCl soln showed a markedly reduced increase in plasma prolactin after restraint when values were compared with those receiving tap water. OVX-PEP-ADX rats receiving daily injections of 0.2 ml corn oil and drinking saline did not respond to restraint. Animals given either 2 or 4 mg corticosterone/day failed to show increased prolactin levels after restraint. Corticosterone levels after restraint were higher than initial values in all of the experiments. The results indicate that prolactin concentrations are regulated by a number of distinctly different conditions. (29 Refs)

**69. STRESS-RELATED FACTORS IN THE NEOPLASTIC PROCESS. (MEETING ABSTRACT).**

Santisteban GA, Riley V, Spackman D

Pacific Northwest Res Fndn, and The Fred Hutchinson Cancer Res Center, Seattle, WA, 98104.

Proc Am Assoc Cancer Res; 18:172 1977

The earliest detectable objective parameter associated with the stress syndrome in the rodent is plasma corticosterone (CSR) elevation. This corticoid elevation is followed by decreased numbers of circulating T and B cells, thymus involution, and weight loss in lymph nodes and spleen, and under some conditions, impairment of mouse immunological and surveillance capacities. Thus any sustained elevation of CSR may trigger physiological events that are capable of altering immunocompetence and neoplasia. Recent work in our laboratory has demonstrated that conventional animal facilities and standard animal handling procedures are inherently stressful and thus capable of altering experimental results, since plasma CSR values of such animals are 100 to 500 ng/ml compared with 30 to 60 ng/ml for quiescent animals maintained in protective facilities. Exposure of mice to the established stress of a population cage, where chronic psychosocial confrontations occur, produces animals with similar high levels, ranging from 200 to 600 ng/ml. This controlled chronic stress induces hypertension, cardiovascular lesions, and increased vulnerability to virus infections and latent neoplasia. Imitation of stress by the direct administration of corticoids, enhances certain experimental neoplastic processes and provides a practical model for examining the mechanisms of stress-associated malignancies. (Author Abstract)

**70. INFLUENCE OF STRESS ON CANCER (LETTER TO EDITOR).**

Riley V
Dept. Microbiology, Pacific Northwest Res. Foundation, Seattle, WA 98104
Science; 193(4247):75 1976

The effect of stress on the thymus and on circulating T and B cells deserves serious attention from investigators. When mice are maintained under conventional housing conditions and handled in the usual manner, they are under constant or intermittent stress. The consequences of this stress are plasma corticosterone values that are 2-10 times higher than normal, accompanied by thymus involution and lymphocytopenia. Because of the role of the thymus and T cells in the immunological process, such animals are abnormal and probably unsatisfactory for experiments that require a known immunological status. The potential use of vitamin A or other suitable substances that might effectively block the dangerous aspects of stress is of great importance. (3 refs)

**71. IMMUNITY, EMOTIONS AND STRESS: WITH SPECIAL REFERENCE TO THE MECHANISMS OF STRESS EFFECTS ON THE IMMUNE SYSTEM.**

Solomon GF, Amkraut AA, Kasper P
Stanford Univ. Sch. Med., Stanford, CA
Ann Clin Res; 6(6):313-322 1974

The effects of stress and emotional distress on the functioning of the immunologic system and the development of cancer and autoimmune diseases are reviewed. Evidence from a variety of sources suggests that stress and emotional distress may relate to dysfunction and hypofunction of the immunologic system. Some forms of stress reduce primary and secondary antibody responses to low-dose antigen stimulation in rats, and adult immunologic responsivity may be altered by early infantile experience. Mixed-sex group housing at high male:female ratios increases the severity of adjuvant-induced arthritis in the male rat and graft-versus-host (GVH) reactions are diminished by food-limitation stress in recipient animals. Sex-segregated group-housed mice show larger murine virus-induced sarcomas when inoculated at six and nine months of age than males housed individually with two or more females. Electric shock stress for three days prior to inoculation with virus reduces the incidence and size of murine sarcoma virus tumors, while shock administered three days following inoculation increases tumor size. Female mice which develop spontaneous fighting behavior show significantly greater resistance to Moloney murine sarcoma-virus tumors. Acutely ill schizophrenic patients with relatively high levels of IgA and IgG have a poorer short-term prognosis and electrolytic lesions of the ventromedial and posterior nuclei of the hypothalamus of recipient and possibly donor animals impair the GVH reaction. Stress and central nervous system lesions also appear to affect thymus-derived lymphocytes and play a role in cell-cell interaction or the release of mediators from reacting lymphocytes. Future studies may indicate that stress affects the macrophage, a hormone-sensitive cell which plays a role in afferent, central and efferent limbs of the immune system.

**72. INFLUENCE OF COMMON ENVIRONMENTAL FACTORS UPON THE NEOPLASTIC PROCESS (MEETING ABSTRACT).**

Santisteban G, Riley V, Spackman DH, Dennis M, Grytting A, Fitzmaurice MA
Pacific Northwest Res. Foundation, Seattle, WA, 98104
Proc Am Assoc Cancer Res; 19:57 1978

Various environmental factors have been examined for their influence upon host physiology and cancer processes in mice. These include: protective, low-stress housing compared with conventional facilities; effects of animal population density in plastic cages; hanging wire-bottom cages compared with plastic cages containing bedding; effect of standard animal handling procedures; and a comparison of the presence or absence of both sexes in the same vicinity. Although such environmental components usually do not have a high priority in experimental design, the results of the studies demonstrate that conventional housing is stressful, as exhibited by a two- to four-fold increase in plasma corticosterone; that wire-bottom cages cause a two-fold increase in such stress-hormones; and that caging male and female mice together induces an enhanced psychosocial stress that is readily measured by elevations of plasma corticosterone. These, as well as other stressful conditions, alter the physiological state of experimental animals by causing an elevation of plasma corticoid, a T cell lymphocytopenia, thymus involution, and impairment of immunocompetence, all of which may have undesirable consequences upon the experimental response of the animal, and increase the difficulties of interpreting the data. The further relevance of such factors to good experimental design includes the observation that mild stress may induce an anorexia and a reduced caloric intake which influences host physiology and metabolism, and alters the neoplastic process.

**73. CANCER-STRESS STUDIES: THE EFFECTS OF PREGNANCY ON PLASMA CORTICOSTERONE AND IMMUNE SYSTEM COMPONENTS IN MICE. (MEETING ABSTRACT).**

Spackman D, Riley V
Pacific Northwest Res. Fndn and Fred Hutchinson Cancer Res. Center, Seattle, Wa. 98104
Proc Am Assoc Cancer Res; 18:172 1977

Our previous studies have demonstrated the deleterious effects of high sustained levels of plasma corticosterone (CSR) on immune system components (thymus, lymphocytes, etc.) and on tumor incidence, growth, and regression in mice. The present studies were designed to determine the effects of pregnancy on plasma CSR and subsequent effects on immune system tissues and cells. We have found that during pregnancy, plasma CSR rises to extremely high levels. In quiescent normal female mice (in protective housing) CSR values are 30-60 ng/ml (A.M.), and under mild stress, rise to 400-600 ng/ml. In pregnant mice, 6 to 48 hrs prior to delivery, CSR values are all above 1000 ng/ml, and have been as high as 1900 ng/ml in BDF and 2700 in C3H mice. In such mice a standard stress has produced increases in CSR to 2800 ng/ml (BDF) and 3600 ng/ml (C3H), thus demonstrating a 100-fold elevation over normal levels. A column chromatographic separation of components (from 50 mul of plasma) has shown the above elevations to be entirely CSR. Since in normal mice, stress elevations of CSR to 400-600 ng/ml cause immune system and tumor growth changes, we are investigating whether similar changes occur in pregnant mice, and if not, the nature of the protective mechanism. Studies are continuing on pregnancy effects on lymphocytes, thymus, and other tissues, and on tumor alterations. (Author Abstract)

**74. EFFECT OF O,P'-DDD ON SECRETION OF 11- AND 17-HYDROXYCORTICOSTEROIDS IN DOGS DURING STRESS.**

Reznikov AG, Kravtsova EL
Kiev Sci. Res. Inst. Endocrinol. Metabol., USSR
Patol Fiziol Eksp Ter; 14(4):38-40 1970

Stress caused by anesthesia and surgery in dogs increased plasma levels of 11- and 17-hydroxycorticosteroids (OCS), hydrocortisone and corticosterone in the adrenal vein. This increase was probably due to the use of morphine, which activates secretion of ACTH, as an anesthetic along with sodium pentobarbital. Preliminary feeding of o,p'-DDD (25 mg/kg/wk) for 7 d before surgery significantly decreased the plasma levels of these steroids. A chromatographic method for separation of hydrocortisone and corticosterone is described.

**75. DERANGEMENTS OF BIOSYNTHESIS, PRODUCTION AND SECRETION OF MUCUS IN GASTROINTESTINAL INJURY AND DISEASE.**

Glass GB, Slomiany BL

Gastroenterology Res. Lab., Dept. Medicine, New York Medical Coll., New York, NY 10029

Adv Exp Med Biol; 89:311-349 1977

The effects of anti-inflammatory drugs (phenylbutazone, aspirin, indomethacin, and corticosteroids), alcohol, stress, and gastrointestinal disease on mucus production and secretion in the gastrointestinal mucosa are reviewed. The effects considered are quantitative and qualitative changes in mucus, increased shedding of the mucus-containing surface epithelial cells and excessive extrusion of cell mucus, and abnormalities in mucus glycoprotein synthesis. Derangements in mucus production and glycoprotein synthesis are described for ulcerative colitis, Crohn's disease, celiac disease, cystic fibrosis, Whipple's disease, and gastrointestinal cancer. The presence of tumor-specific antigens in human gastrointestinal cancer is considered. (170 Refs)

**76. SURFACE PROPERTIES OF LYMPHOID CELLS - SUMMING UP. (PP. 159-162)**

Schlesinger M

Immune Reactivity of Lymphocytes Development, Expression, and Control. Feldman M, Globerson A, ed. New York, Plenum Press, Advances in Experimental Medicine and Biology; vol. 66, 1976.

Papers on the surface properties of lymphoid cells are briefly reviewed. The thymus of AKR leukemic mice shows an increase of the minor thymic population, possessing a relatively low theta-antigenicity and high H-2 antigenicity. The responsiveness of the human thymus cells to phytohemagglutinin and concanavalin A increases markedly with age. The proportion of thymus cells forming stable E-rosettes in man decreases with age. Thymus subpopulations also differ in their capacity to stimulate mixed lymphocyte reactions; the thymus undergoes involution under various conditions such as stress, administration of corticosteroid hormone, cancer, or administration of LPS. There is an enormous heterogeneity among T lymphocyte subpopulations; the heterogenity of the cell surface properties appears to be correlated with a heterogeneity of their functional capacities. (10 refs)

**77. NUTRITIONAL DEFICIENCY, IMMUNOLOGIC FUNCTION, AND DISEASE.**

Good RA, Fernandes G, Yunis EJ, Cooper WC, Jose DC, Kramer TR, Hansen MA

Mem Sloane-Kettering Cancer Ctr, NY, NY 10021

Am J Pathol; 84(3):599-614 1976

Several experiments conducted by our group over a period of 6 yr have shown that nutritional stress, especially protein and/or calorie deprivation, leads to many, often dramatic, changes in the immune responses of mice, rats, and guinea pigs. Chronic protein deprivation (CPD) has been shown to create an enhancing effect on the cell-mediated immune responses of these animals. Humoral responses under CPD conditions were most often found to be depressed, but sometimes were unaffected, depending on the nature of the antigen employed. Chronic protein deprivation, consistent with the pattern just mentioned, improved tumor immunity by depressing production of B-cell blocking factors, and, in at least one instance, resistance to development of mammary adenocarcinoma in C3H mice was associated with evidence of increased numbers of T suppressor cells. Profound nutritional deficits ( less than 5% protein per total daily food intake) depressed both cellular and humoral immunity. Early, though temporary, protein deprivation caused a long-term depression of both cellular and humoral immunity also, with the humoral component being the first to recover. Manipulation of protein and calories was found to have a profound effect on certain autoimmune conditions. Diets high in fat and low in protein favored reproduction but shortened the life of NZB mice, whereas diets high in protein and low in fat inhibited development of autoimmunity and prolonged life. Chronic moderate protein restriction permitted NZB mice to maintain their normally waning immunologic functions much longer than mice fed a normal protein intake. Further, the low-protein diet was associated with a delay in development of manifestations of autoimmunity. Decreasing dietary calories by a reduction of fats, carbohydrates, and proteins more than doubled the average life span of (NZB X NZW)F1 mice, a strain prone to early death from autoimmune disease. Histopathologic studies using immunofluorescent microscopy revealed that the development of the renal lesions caused by the deposition of antigen-antibody complexes, which is so characteristic of these mice, was markedly delayed. (Author Abstract)

**78. INHIBITION OF TUMOR INITIATION AND PROMOTION BY ANTI-INFLAMMATORY AGENTS.**

Slaga TJ, Scribner JD

Fred Hutchinson Cancer Res Ctr., Seattle, Wash.

J Natl Cancer Inst; 51(5):1723-1725 1973

Two nonsteroidal anti-inflammatory agents, Tandearil, 1-phenyl-2-(p-hydroxyphenyl)-3,5-dioxo-4-n-butylpyrazolidine monohydrate and W2354, 7-chloro-3,3a-dihydro-2H-isoxazolo (3,2-b)(1,3-benzoxazin-9-one), greatly reduced, but did not completely suppress, tumor promotion in the skin of female Charles River CD-1 mice caused by the croton oil factor 12-0-tetradecanoylphorbol-13-acetate (TPA). The steroidal anti-inflammatory agent, dexamethasone, markedly reduced tumor initiation by 3-methylcholanthrene (MCA) and reduced complete carcinogenesis by MCA. The previously noted weight loss caused by dexamethasone treatment did not occur with the nonsteroidal anti-inflammatory agents. Tandearil also lacked the immunosuppressant activity of dexamethasone and the effects of dexamethasone on the adrenal-pituitary system. The studies conducted suggest that complete carcinogenesis by MCA consists of a continuing summation of initiated cells, propagated by the mild hyperplasia produced by the carcinogen. It is therefore suggested that small amounts of hydrocarbon combined with a continuing promoting stress may be much more damaging to the population than much larger amounts of hydrocarbon in the absence of promoters. The reduction of various pollutants in the human environment is urged.

**79. APPARENT T CELL FUNCTION OF BONE MARROW CELLS FROM MICE EXPERIENCING A GRAFT-VERSUS-HOST REACTION.**

Elie R, Lapp WS

Departement de Sciences Biologiques, Universite de Quebec a Montreal, Montreal, Canada

Cell Immunol; 21(1):185-191 1976

The graft-versus-host (GVH) reaction, induced in adult F1 mice (strain B6 x A) by the injection of parental strain lymphoid cells (GVH mice), suppressed the in vitro plaque-forming cell (PFC) response to SRBC of spleen cells obtained from the GVH mice (GVH-SC); in vitro restoration of the PFC response of GVH-SC was performed with a modified Marbrook culture chamber consisting of an inner culture compartment (IC) separated from an outer culture compartment (OC) by a cell-impermeable membrane. Thymus cells (TC) and lymph node cells (LNC) but not bone marrow cells (BMC) from normal mice placed in the IC restored the PFC response of GVH-SC cultured with SRBC in the OC. The restoring ability of TC and LNC was markedly reduced following treatment with anti-theta serum plus complement. BMC taken from GVH mice three or more days post-GVH

induction (GVH-BMC) and placed in the IC restored the PFC response of GVH-SC as well as TC and LNC. Treatment of GVH-BMC with anti-theta serum plus complement did not affect their restoring ability; furthermore, the number of theta-bearing cells in the bone marrow did not increase as a consequence of the GVH reaction. Two possible explanations were proposed for the T-like function of GVH-BMC: that the stress of the GVH reaction could increase the production of corticosteroid hormones and cause T cells to be sequestered in the bone marrow; or that the GVH reaction activates potential T cells in the bone marrow.

## B. Modification of the Effects of Environmental Stress by Fat-Soluble Vitamins

### 80. MODIFICATION BY VITAMIN A OF ADRENAL AND THYMUS RESPONSES IN SKIN-GRAFTED, TUMOR-BEARING, OR OTHERWISE STRESSED MICE (MEETING ABSTRACT).

Seifter E
Albert Einstein College of Medicine, New York, N. Y. 10461
Proc Am Assoc Cancer Res; 17:98 1976

Skin grafts, tumors (MuSV-M; C3HBA), and a variety of other stresses cause an increase in adrenal weight and a corresponding decrease in thymus weight. This may be expected to depress cellular immunity mechanisms. Supplementation of the diet with moderate doses of vitamin A (37,500 to 150,000 units/Kg) reduced adrenal enlargement and thymic shrinkage in such animals; it accelerated skin graft rejection. In normal animals, it caused thymic hypertrophy. With regard to the sarcoma, vitamin A delayed or prevented tumor appearance, inhibited tumor growth, and accelerated regression. With regard to the mammary adenocarcinoma, vitamin A again prevented or delayed tumor appearance, slowed tumor growth, and prolonged survival. Cortisone administration enhanced takes, growth, and severity of both tumors; vitamin A administration lessened these cortisone actions. Desoxycorticosterone , in contrast to cortisone , markedly delayed tumor appearance and greatly prolonged survival; it inhibited metastasis of the carcinoma. We suggest that vitamin A antiglucocorticoid action results in part from a shift in the balance of adrenocorticoid secretion from gluco- to mineralocorticoids. Preliminary studies on circulating adrenocorticoids are compatible with this possibility. (Author Abstract)

### 81. VITAMIN A: ACTIONS IN ONCOGENESIS AND SKIN GRAFT REJECTION.

Rettura G, Levenson SM, Schittek A, Seifter E
Albert Einstein Coll. Medicine of Yeshiva Univ., Bronx, NY
Surg Forum; 26:301-303 1975

The influence of the casting procedure on the graft rejection, the influence of vitamin A on this reaction, the action of vitamin A in tumor-bearing mice with casts, and the effect of skin grafting on Moloney 206 murine sarcoma virus (MSV) tumor growth were studied. Female C3H/Hej mice (6-wk-old) were grafted with donor skin from C57Bl females and inoculated with 0.1 ml im of 10**-2, and 10**-3 MSV. Some mice received casts and some were given po vitamin A palmitate. Graft survival was directly related to the length of time the cast was carried: the cast was thus immunosuppressive. Vitamin A decreased graft survival time in mice carrying the cast for more than 9 days. Stress associated with casting increased tumor incidence in mice inoculated with low viral inocula but inhibited tumor regression in mice given the high viral inocula. Vitamin A markedly reduced the effects of casting. Grafting enhanced tumor growth and prevented tumor regression. Thus, grafting and casting are immunodepressive as is MSV inoculation. The immunodepression required to maintain graft survival was sufficient to stimulate growth. Vitamin A stimulated immunity against both the graft and tumor. (2 refs)

### 82. EFFECT OF VITAMIN A ON TUMOR DEVELOPMENT IN BURNED, UNBURNED, AND GLUCOCORTICOID-TREATED MICE INOCULATED WITH AN ONCOGENIC VIRUS.

Levine NS, Salisbury RE, Seifter E, Walker HL, Mason AD, Pruitt BA
U. S. Army Inst. Surg. Res., Brooke Army Med. Cent., Fort Sam Houston, Texas
Experientia; 31(11):1309-1312 1975

The effect of high dose vitamin A (1 wk of a diet containing 12 IU/g vitamin A and drinking water containing 150 U/ml Aquasol A) on burn-stressed (25% of the body surface area), glucocorticoid-treated (Solu-medrol, 1 mg, s.c) and normal animals was studied in 7-wk-old male CBA mice inoc with Moloney sarcoma virus. Vitamin A significantly reduced peak tumor size and accelerated tumor regression in sham-burned control animals but did not affect these parameters in burned animals. Mice receiving a single dose of Depo-Medrol 48 hr prior to virus inoc developed larger tumors than control mice not receiving steroids, and vitamin A did not affect tumor growth in the steroid-treated mice. It is suggested that the laboratory diet for the mouse provides insufficient vitamin A to maintain lymphoid elements at optimum levels of function. (20 refs)

### 83. EFFECT OF VITAMIN A DEFICIENCY ON INTESTINAL CELL PROLIFERATION IN THE RAT.

Zile M, Bunge EC, DeLuca HF
Dept. Biochemistry, Coll. Agricultural and Life Sciences, Univ. Wisconsin-Madison, Madison, WI 53706
J Nutr; 107(4):552-560 1977

The effect of vitamin A deficiency on the cell division kinetics and biochemical composition of the small intestine of weanling male Holtzman rats was determined. The rats were further divided into those who received no vitamin A and those who received retinol (10 or 20 ug po every 2 days). The growth rate of the deficient rats started to decrease after they had been fed the diet for 5-6 wk. Within 1 wk, their wt had plateaued or decreased. At the time of sacrifice, no vitamin A could be detected in the livers of the deficient rats and their serum levels were less than one-third of normal. Grossly, the intestinal length and jejunal mucosa appeared unaffected. The generation time for the jejunal crypt cells was 1.5 hr longer in deficient rats than in vitamin A-supplemented rats, mainly as a result of an increase in the S phase by 1.5 hr. The duration of G1 and G2 + M was not affected. The labeling index of the jejunal crypts of deficient and normal rats was essentially the same. However, the proportion of labeled cells in the crypts of normal rats remained constant until the onset of the second cell division, whereas the proportion of labeled cells in the crypts of deficient animals increased after 1.5 hr until 47% to 49% of the cells were labeled by 6 hr. There was no significant difference between the two groups with respect to growth fraction or overall biochemical composition of the jejunal mucosa. Since vitamin A is essential for the replacement of intestinal cells, the tissue of the deprived animal may have an impaired ability to withstand exogenous stresses. (35 Refs)

### 84. DIFFERENTIAL RESPONSES TO RETINOL AND RETINOIC ACID (MEETING ABSTRACT).

Seifter E, Rettura G, Weinzweig N, Levenson SM
Albert Einstein Coll of Med, Bronx, NY 10461
Fed Proc; 36(3):1102 1977

We have compared all trans vit A alcohol with all trans vit A acid in several systems. In CBA mice, vit A acid (25mg/kd

diet) inhibits growth and causes weight loss. At 50mg/kg diet, vit A acid causes severe weight loss. This toxicity is not seen in mice fed as much as 200mg/kg diet of vit A. Vit A does not enahnce or diminish the toxicity of these levels of retinoic acid. These and higher levels of retinoic acid were lethal to mice inoculated with Moloney sarcoma virus, whereas all levels of vit A showed a dose-dependent anti-tumor activity. Levels of vit A acid generally used in animal tumor studies caused adrenal hypertrophy and thymic involution. In normal mice, comparable levels of vit A had the opposite effect. In mice subjected to stress or MSV tumors, vit A caused further weight loss and thymic involution, in contrast to the protective actions of vit A. Vit A shares one toxic property with its analogs, ie disruption of lysosomal membranes. While this property accounts for most of the anti-tumor action of the analogs, this is not so for vit A which acts via macrophage mobilization, inhibition of the stress reaction and stimulation of thymic regeneration. The area of overlap between the actions of vit A and its analogs is small compared to their vital differences. We think that the term hypervitaminosis A should not be applied to the toxicity due to vit A analogs. (Author Abstract)

**85. OF STRESS, VITAMIN A, AND TUMORS.**

Seifter E

Dept. Biochemistry, Albert Einstein Coll. Medicine, Yeshiva Univ., Bronx, NY 10461

Science; 193(4247):74-75 1976

Evidence in favor of the hypothesis that increased tumor development in stressed mice is due to adrenal cortical hypersecretion of corticosterone is presented. Stress increased the incidence and severity of tumor development in mice inoculated with a murine sarcoma virus (MuSV-M). The influence of stress on thymic size and cellularity was also demonstrated, and stress-reduced immunocompetence was hypothesized to be the result of increased adrenal corticosterone secretion. Metyrapone, a chemical which inhibits corticosterone production, prevented the typical stress reaction of adrenal hypertrophy and thymic involution and increased the resistance of stressed and nonstressed mice to MuSV-M. Steroids such as deoxycorticosterone, which can compete with corticosterone for some tissue receptor sites, also prevented the adverse effect of stress in mice inoculated with MuSV-M. Vitamin A, which blocks some host responses to stress or cortisone administration, was remarkably protective against both thymic involution and tumor development following the inoculation of mice with MuSV-M. Vitamin A, employed without any other chemotherapeutic agent, also inhibited the growth of C3HBA transplanted tumor cells. (8 refs)

**86. VITAMIN A AND LUNG CANCER (LETTER TO EDITOR)**

Critselis AN, Rettura G, Seifter E

Dept. Surgery, Albert Einstein Coll. Medicine, Bronx, NY

Br Med J; 2(6049):1450 1976

A journal letter examines the relation between low vitamin A levels and bronchial carcinoma. It is still controversial whether an excess of vitamin A gives an antitumor effect, whether the host experiences an increased need for the vitamin in the presence of a carcinogen, or whether the susceptibility of the host to the carcinogen is inversely proportional to vitamin intake. Low vitamin levels might impair immune responses normally active against a critical number of transformed cells. Stress situations elicit vitamin A losses by inducing ACTH over-secretion and increased glucocorticoid production, which favors vitamin A excretion. (10 refs)

**87. PROTECTION OF ENVIRONMENTALLY STRESSED HUMAN CELLS IN CULTURE WITH FREE RADICAL SCAVENGER, DL-A-TOCOPHEROL. (PP. 519-535)**

Packer L

Aging, Carcinogenesis, and Radiation Biology. The Role of Nucleic Acid Addition Reactions. Smith KC, ed. New York, Plenum Press, 1976.

The extent to which the life span of normal human (WI-38) cells in culture is a genetically-determined or environmentally-limited phenomenon is considered. Particular emphasis is placed on free-radical damage to membranes containing biological oxidation catalysts or environmentally-induced free radicals. Free-radical mediated oxidative damage of membrane lipids may be averted by the naturally-occurring free-radical scavenger, vitamin E, and may increase the potential of WI-38 cells growing in culture to proliferate both under conditions of normal aging obtained in the in vitro culture environment and upon exposure to certain types of environmentally-induced damage. The effects of several different types of environmental and/or nutritional stresses were studied: starvation, gases (oxygen and pollutants) and riboflavin-photosensitized damage. In each case the protective effects of dl-alpha-tocopherol in protecting WI-38 cells from lethal effects were evaluated. Vitamin E protected the cells from riboflavin-photosensitized damage and apparently from starvation damage; the latter case was only if in conjunction with dl-alpha tocopherol, which was effective in protecting the cells from oxygen toxicity.

# VI. THE ROLE OF ENVIRONMENTAL STRESS IN THE EXPERIMENTAL INDUCTION OF CANCER

## A. Interaction of Chemical or Physical Carcinogens and Stress: Inhibition of or No Effect on Tumor Growth

**88. INHIBITION OF HUGGINS TUMORS BY FORCED RESTRAINT.**

Newberry BH, Gildow J, Wogon J, Reese RL

Dept. Psychology, Kent State Univ., Kent, OH 44242

Psychosom Med; 38(3):155-162 1976

Three experiments demonstrated that chronically administered restraint inhibits the development of DMBA-induced rat mammary tumors. The manipulation involved the confinement of female Sprague-Dawley rats in hardware cloth tubes. This retraint resulted in a lower proportion of positive responses, increased latency of tumor development, and lower number of tumors in positive animals when restrained animals were compared with controls. Organ weights failed to show a stress response. Organ weight data from experiment II also failed to demonstrate a stress response. Molar activity data from experiment III indicated that early in the experiment activity increased among the restrained animals on release from restraint. Two measures of activity were used, direct observation of molar activity and a crystal accelerometer. The activity data indicated significant differences between the restraint and non-restraint conditions. A fourth experiment, which employed a crystal accelerometer to assess activity, produced a similar activity pattern and also provided evidence of adrenal ascorbic acid depletion as a function of restraint. (26 refs)

**89. INHIBITORY EFFECTS OF STRESS ON EXPERIMENTAL MAMMARY TUMORS (MEETING ABSTRACT). (PP. 39-40)**

Newberry BH
Kent St Univ, Kent, OH 44240
Third International Symposium On Detection And Prevention Of Cancer. 1976.

A number of studies dealing with the effects of 'stressful' conditions on DMBA-induced rat mammary tumors have been carried out. Tumor induction has been by caudal IV injection of an emulsion containing DMBA at 50-56 days of age (total dose = 6 mg). The original experiments employed a regimen of severe electric shock, which significantly inhibited tumor development. Subsequent studies using forced restraint produced the same results. The effect of these treatments appears as an increase in induction latency, a reduction in the proportion of animals developing palpable tumors, and a reduction in the number of palpable tumors developed by positives. There is no significant effect on the mean size of the tumors. Later studies, concerned with the timing of the restraint treatment relative to the induction period, indicate that the inhibitory effect is largely, if not completely, on the proliferation of neoplastic cells rather than on their initiation by the carcinogen: Restraint applied before or during the induction period produced no inhibitory effect, while restraint applied after DMBA clearance was effective. Two restraint experiments included assessments of activity. These studies indicated some increase in activity as a function of restraint, but the timing and amount of the increase were not such as to suggest that muscular activity or fatigue mediates the inhibitory effect. There is little evidence for a severe prolonged pituitary-adrenocortical response to the restraint treatment. (Author Abstract)

**90. EFFECTS OF STRESS ON GROWTH OF TRANSPLANTED AND 7,12-DIMETHYLBENZAANTHRACENE-INDUCED TUMORS AND THEIR MODIFICATION BY PSYCHOTROPIC DRUGS.**

Pradhan SN, Ray P
Dept. Pharmacol., Howard Univ. Coll. Med., Washington, D.C.
J Natl Cancer Inst; 53(5):1241-1245 1974

The effects of various types of stress (immobilization, sound, electric foot-shock, and electroconvulsive shocks) on the growth of transplanted 4M mammary carcinoma in Sprague-Dawley male littermate rats and 7,12-dimethylbenzaanthracene-induced tumors in Sprague-Dawley female littermate rats were investigated. Tumor growth was inhibited concomitant with an increase in adrenal wt and decrease in spleen wt. Pretreatment with chlorpromazine reduced or abolished the inhibition of tumor growth in the stressed rats; pretreatment with imipramine had less effect. Neuro-endocrine and other mechanisms appeared to be involved. (35 refs)

**91. EFFECT OF STRESS ON THE ADRENOCORTICOLYTIC AND CARCINOGENIC ACTION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.**

Somogyi A, Kovacs K
Inst. Med. Exp. Surg., U. Montreal, Quebec, Canada
Z Krebsforsch; 75(4):288-295 1971

Female rats were exposed to stress before and after administration of either 7,12-dimethylbenz(a)anthracene (DMBA), or 7-hydroxymethyl-12-methylbenz(a)-anthracene (7-OHM-MBA). 'Stress' consisted of forced muscular exercise lasting for 6.5 hr, or forced muscular restraint lasting for 17 hr. Although stress did not increase the incidence of adrenal lesions in rats given 4 mg DMBA, it was found that lesions which did appear in rats undergoing exercise stress prior to DMBA treatment were more severe than those appearing in rats not subjected to stress. The adrenal necrotic effect produced by 7-OHM-MBA was also potentiated by stress. Adrenal lesion incidence increased in rats given 2 mg of DMBA and prior exercise stress compared to rats given DMBA and no stress. In rats given 2 mg DMBA and restraint stress, spirolactone treatment nearly abolished the aggravation by stress of DMBA-adrenocorticalysis, while spirolactone had no such effect in rats given 4 mg of DMBA and restraint. In turn, stress was able to counteract the adrenal protection from the effects of DMBA afforded by spirolactone. The mammary carcinogenic effect of DMBA was not affected by stress.

**92. GROWTH OF TRANSPLANTED AND INDUCED TUMORS IN RATS UNDER A SCHEDULE OF PUNISHED BEHAVIOR.**

Ray P, Pradhan SN
Howard U. Coll. Med., Washington, D. C.
J Natl Cancer Inst; 52(2):575-577 1974

Sprague-Dawley rats with transplanted 4M mammary carcinoma (0.2 ml saline suspension of minced tumor injected sc) or tumors induced by 7,12-dimethylbenz(a)anthracene (20 mg by intragastric instillation) were placed on a schedule of punished (conflict) behavior in which food reinforcement was paired with mild electric shock. This behavioral stress inhibited growth and development of both the transplanted and induced tumors. The role of neuroendocrine factors in stress-induced alteration in tumor growth is discussed. Behavioral stress with psychosomatic involvement may alter homeostatic functions mediated through neuroendocrine mechanisms and cause hormonal imbalance. Such imbalance may be characteristic of the stage of resistance (adaptive) or the stage of exhaustion (maladaptive) of the General Adaptation Syndrome of Seyle. Inhibition of tumor growth in this study appeared indicative of the stage of resistance.

**93. EFFECT OF AUDIOGENIC STRESS UPON METHYLCHOLANTHRENE-INDUCED CARCINOGENESIS IN MICE.**

Molomut N, Lazere F, Smith LW
Waldemar Med. Res. Found., Inc., Port Washington, N. Y.
Cancer Res; 23(7):1097-1101 1963

DBA/1 (audiogenic seizure-susceptible) and A/Jax (seizure-resistant) mice were subjected to bell-ringing sound and an approx. 80-90% effective carcinogenic dose of 20-methylcholanthrene and observed for time of tumor induction and ultimate fate. There was a delay in the time of tumor induction (latent period) in DBA/1 mice subjected to audio stimulus as compared with DBA/1 controls, whereas A/Jax mice were unaffected. Despite the delayed tumor induction in sound-stimulated DBA/1 mice, their survival time was the same as comparable controls. It is believed that, once induced, the tumor cell growth was stimulated by the sound stress exposure. No significant differences in carcinogenesis were noted when cortisone was admin in lieu of sound stress. The addition of cortisone to sound stress exposure significantly reduced the tumor induction in the DBA/1 mice (58%), whereas tumor induction in A/Jax mice was 100%, a slight increase over A/Jax controls.

**94. INCIDENCE OF LYMPHATIC LEUKEMIA AND METHYLCHOLANTHRENE-INDUCED CANCER IN LABORATORY MICE SUBJECT TO STRESS.**

Kaliss N, Fuller JL
Jackson Lab., Bar Harbor, Me.
J Natl Cancer Inst; 41(4):967-983 1968

The leukemia incidence was studied in AKR/J mice (both sexes) stressed by repeated electroshock (or equivalent handling) or crowding and in (AKR/J x DBA/2)F1 mice undergoing repeated audiogenic seizures. Carcinogenesis by I

inj of 3-methylcholanthrene (0.25 mg sc in triotanoin) was studied in C57BL/6J mice treated by electroshock and in (C57BL/6J x DBA/2)F1 mice treated by audiogenic seizures. The stressors did not significantly affect the tumor incidence, although changes in body wt gain, rectal temperature and activity were noted.

**95. VARIATIONS IN THE RATE OF INDUCTION OF CHEMICAL CARCINOGENESIS ACCORDING TO DIFFERING PSYCHOLOGICAL STATES IN RATS.**

Anderson MR
Algernon Firth Inst. Path., Leeds, England
Nature (Lond); 204:55-56 1964

Four groups of 12 Sheffield strain male and female wistar rats were inoc sc with 20-methylcholanthrene (0.05 g). Each group was then maintained in a different environmental condition as follows: group A (contented) was stroked daily; group B (stressed) received daily inj of epinephrine; group C (alerted) was kept in tension cages which were lit for 5 min preceding an electric shock delivered to the floor of the cage once every hr; group D (controls) received no further treatment. After 40 wk, the number of female and male rats, resp, without tumors in each group was: (A) 0/6 and 0/6; (B) 2/5 and 0/6; (C) 3/6 and 1/6; (D) 0/6 and 0/6. It is believed that the rate of tumor induction by chemical carcinogenesis in rats can be varied by modifying the environment, and hence the psychological state.

**96. BIOLOGICAL EFFECT OF STRESS FOLLOWING IONIZING RADIATION.**

Gambino JJ, Bennett LR, Billing MS, Lamson BG
Dept. Radiol. Path., U. California Sch. Med., Los Angeles
Aerosp Med; 35(3):220-224 1964

The effects of repeated stress-producing stimuli following sublethal irradiation was studied in 4-month-old female Long-Evans rats: 61/195 (Group 1) received whole body X-irradiation (500 r); 70/195 (Group 2) received beta-irradiation (500 r) of the surgically exposed adrenal glands; 64/195 (Group 3) served as nonirradiated controls. Surviving animals, 4 mo after irradiation, were either exposed to intermittent cold (3 hr./day at 0 degree plus or minus 1 C) or kept at a temperature of 25 C plus or minus 2 C. There was no significant difference in the number of palpable tumors in cold- and normal-temperature-treated rats of Group 1; however, there was a lower percentage of tumor-bearing rats among cold-treated animals (56 as compared to 71) which after 17-18 mo was significant at the 5% level. In Group 2, the percentage of tumor-bearing rats and total tumors was 44 and 66, resp, for animals exposed to normal temperatures and 37 and 48 resp, for those exposed to cold. As compared to controls, animals of Group 2 showed slightly accelerated mammary gland enlargement and appearance of palpable tumors.

**97. THE INFLUENCE OF A CHRONIC ENVIRONMENTAL STRESS ON RADIATION CARCINOGENESIS.**

Baker DG, Jahn A, Hollander CF
Mount Zion Hospital and Medical Center, San Francisco, CA 94120
Proc Am Assoc Cancer Res; 16:55 1975

The influence of a chronic environmental stress on the incidence of radiation induced tumors, lens opacities and survival times was determined. Female CFN rats were exposed to whole body irradiation with either 300 rads of fission neutrons, 600 rads of 250 kv X-rays, or sham irradiation. Within each irradiated group, rats were assigned to one of four environments: exposure to 25 degrees C until irradiated and immediately returned to (1) a 25 degrees C or (2) a 2 degrees C environment for duration of life; acclimation to a 2 degrees C environment for 40 days, irradiated, then returned to (3) a 2 degrees C or (4) a 25 degrees C environment. Post irradiation exposure to the 2 degrees compared to the 25 degrees C environment, reduced tumor incidence in the X- and neutron irradiated groups, but reduced incidence of lens opacities only in the neutron irradiated group. A 2 degrees C environment before and after irradiation produced similar results. Return of the 2 degrees C acclimated rats to a 25 degrees C environment increased incidence of tumors and lens opacities in the X-ray group, but reduced incidence of both in the neutron irradiated rats. Chronic exposure to 2 degrees C reduced the tumor incidence of nonirradiated rats but did not change the incidence of lens opacities. Median life expectancy was reduced by exposure to the 2 degrees C environment. (Author Abstract)

**98. THE INFLUENCE OF A CHRONIC ENVIRONMENTAL STRESS ON RADIATION CARCINOGENESIS.**

Baker DG
Div. Oncologic Radiobiologic Res., Claire Zellerbach Saroni Tumor Inst., Mount Zion Hosp. Medical Center, San Francisco, CA 94120
Radiat Res; 68(3):449-458 1976

The effect of a chronic environmental stress on radiation carcinogenesis is evaluated. Female CFN rats were exposed to whole-body irradiation with either sham irradiation, 600 rads of 250 kilovolt x-rays, or 300 rads of fission neutrons. When rats at 25 C were placed in a 2 C environment immediately after irradiation, there was a significant early mortality. In rats that were first acclimated to cold, then irradiated and returned to the 2 C environment, there was less early mortality and a longer median survival time, compared with the non-cold-acclimated rats. The survival of the rats placed in the 2 C environment at either 6 or 16 days postirradiation was determined. Early mortality in these two groups was reduced compared to rats placed at the 2 C environment immediately after irradiation. This was reflected by an increased median survival time, although the max survival time was not significantly altered as a result of the delay. At the 2 C environment, the incidence of tumors in the sham-irradiated rats was reduced to one-half of that observed in the sham-irradiated rats at a 25 C environment. The percentage of rats in all subgroups that developed tumors after irradiation was increased compared to the incidence in the sham-irradiated rats. In both alpha- and neutron-irradiated rats, exposure to a 2 C environment reduced the tumor incidence to that seen in the sham-irradiated rats at 25 C. When there was a delay of either 6 or 16 days between irradiation and exposure to the 2 C environment, the tumor incidence was reduced to a value below that observed in the sham-irradiated rats at 25 C and, for the 16-day interval, below the incidence found in the sham-irradiated rats at 2 C. In nonirradiated rats, the proportion having lens opacities in one or both eyes was not changed by exposure to the 2 C environment, but was increased when the cold-acclimated rats were returned to the 25 C environment. At the 25 C environment, irradiation increased the incidence of lens opacities. On the basis of radiation dose, neutrons were almost 7.4x as effective as x-rays. Exposure to 2 C immediately after irradiation did not reduce the incidence of lens opacities in the x-ray group, but did reduce the incidence following neutron irradiation. A delay of 6 or 16 days between x-irradiation and transfer to the 2 C environment reduced the incidence of lens opacities. A chronic environmental stress after x- or neutron radiation may inhibit malignant transformation. (22 Refs)

**99. INFLUENCE OF A CHRONIC ENVIRONMENTAL STRESS ON THE INCIDENCE OF METHYLCHOLANTHRENE-INDUCED TUMORS.**

Baker DG

Claire Zellerbach Saroni Tumor Inst., Mount Zion Hosp. and Medical Center, San Francisco, CA 94115

Cancer Res; 37(11):3939-3944 1977

The influence of a chronic environmental stress, ie, living in a 2 C environment, on the incidence of methylcholanthrene (MC)-induced tumors in albino female Simonsen rats, a Sprague-Dawley-derived strain, was studed. The metabolic rate was double for rats kept at 2 C compared with those kept at 25 C. Exposure to 2 C for life, with no other treatment, reduced median life expectancy to 560 days compared with 686 days for rats kept at 25 C. Transfer to a 2 C environment after 250 days at 25 C reduced the incidence of spontaneous tumors, but transfer to 25 C after 250 days at 2 C increased the incidence compared with that for rats always kept at 25 C. Exposure to 2 C immediately following MC administration (2 mg sc) significantly reduced tumor incidence compared with that in rats kept at 25 C but did not change tumor induction time. The reduced tumor incidence may have resulted from inhibition of carcinogenic transformation by chronic stress. The survival time of rats with MC-induced tumors was not significantly less in 2 C environment than it was at 25 C. (28 Refs)

**100. COMBINATION EFFECTS IN CHEMICAL CARCINOGENESIS (EXPERIMENTAL RESULTS).**

Schmahl D

Instituts fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg, West Germany

Oncology; 33(2):73-76 1976

The author reviews investigations of syncarcinogenesis, or the interaction of many environmental carcinogens in inciting malignant tumors. Fundamental parameters necessary for the evaluation of experimental syncarcinogenic effects include tumor incidence, induction time, tumor induction dose, organotropy, tumor histology, and incidence of metastases. When two chemicals with the same organotropy, such as the hepatocarcinogens diethylnitrosamine and 4-dimethylaminoazobenzene, were applied simultaneously to mice or rats in fully effective doses, the additive effect was a shorter induction time. Syncarcinogenesis was not observed, however, when carcinogens of differing organotropy were administered simultaneously. Since the cell types attacked were different, the action of each substance was independent of the other. Administration of an organ-specific carcinogen with another organ-damaging substance did not alter carcinogenesis in the liver, esophagus, or bladder. In other experiments, chemical carcinogenesis was not influenced by exposure of animals to various stimuli, such as stress and physical activity; growth behavior of the tumors was identical to that found in untreated controls. Carcinogens, therefore, may have additive effects, act independently from one another, or show inhibitory effects. (22 refs)

## B. Interaction of Chemical or Physical Carcinogens and Stress: Enhancement of Tumor Growth

**101. EFFECTS OF BRIGHTNESS OR DARKNESS ON CARCINOGENESIS.**

Sakakibara T

Nagoya City U. Med. Sch., Japan

J Nagoya City Univ Med Assoc; 19(2):525-557 1968

Liver tumor induction by a 20-wk course of 3'-methyl-4-dimethylaminoazobenzene feeding (0.06% in diet) was studied in 4 groups of 11-wk-old mice. In mice exposed to flashing lights (1000 lux; switched on and off 30 times/minute for 8 hr./day), liver tumors developed in 15 wk and the tumor incidence (after 14-20 wk) was 78.6%. In mice exposed to fluorescent light (1000 lux) all day, tumors developed in 16 wk and the incidence was 64.3%. In mice kept in darkness, tumors developed in 18 wk and the incidence was 28.6%. In control mice kept under natural room light, tumors developed in 18 wk and the incidence was 35.7%. The increased incidences of liver tumors in mice exposed to flashing or fluorescent light was attributed to a stress response to light. Within each group of animals, the mice developing liver tumors at the earliest times were not significantly different from the other mice (those developing tumors at later times or mice remaining without tumors) with respect to body wt changes or the observed changes in the RBC and WBC levels.

**102. EFFECT OF ROTARY MOTION ON CARCINOGENESIS.**

Suzuki S

Nagoya City U. Sch. Med., Japan

J Nagoya City Univ Med Assoc; 19(4):1517-1558 1969

Rats were admin. 3'-methyl-4-dimethylaminoazobenzene (3MeDAB; 0.06% in the diet) and exposed to rotary motion for 30 min, or 1-2 hours/day. Liver tumors developed in 18-23 weeks in 75% of the rats rotated 2 hours and in 58%, 33% and 25% after 1 hour, 30 min or no rotation, resp. Tumor wt increased for all groups and was max for 2-hour treatment; body wt increase was least for the 2-hour group and greatest in controls. The RBC count decreased as rotation time increased. Figures of WBC count changes were not significant. It is concluded that rotary motion causes stress which stimulates function of the pituitary gland or adrenal cortex, thus, promoting tumor development.

**103. ENHANCING EFFECTS OF PSYCHOSOCIAL STIMULATION ON EXPERIMENTAL MAMMARY TUMORS (MEETING ABSTRACT). (PP. 40-41)**

Cooley B, Henry JP, Stephens PM

Univ So CA, Sch Med, Dept Physiol, Los Angeles, CA 90007

Third International Symposium On Detection And Prevention Of Cancer. 1976.

Repeated daily periods of immobilization or electric shock will inhibit DMBA-induced rat mammary tumors (Newberry et al, Psychosom Med 34:295, 1972). By contrast, force breeding (repeated removal of all young at birth) of females in groups of 3-4 with 1 male reliably enhances rates of mammary tumor formation in mice. Results of preliminary studies with mouse colonies in population cages containing 12 females and 6 males have led to the hypothesis that the pituitary adrenal-cortical depressive reaction may enhance tumor formation, whereas the sympathetic adrenal-medullary response whose activation is based on aggressive perception of repeated predictable stimuli may be inhibitory. Nineteen females, each paired with a single male, were force bred for up to 10 months, starting when 4 months old. Three mammary tumors developed. Of 57 normally bred control females, 29 paired with a single male developed 4 tumors, and 28 bred and maintained alone developed 3. Thus the tumor rate was not elevated in the animals that were force bred. Corticosterone levels tended to be lower in the force-bred group and higher in the aging normal breeder groups. Since this one-to-one method of force breeding does not permit social interaction, the present work suggests that force breeding itself may not be responsible for enhancing the rate of mammary tumor formation. The studies cited above do, however, indicate that the neuroendocrine disturbances that follow depressive as opposed to aggressive psychosocial interactions might play a part. (Author Abstract)

**104. EFFECT OF STRESS ON FORMATION OF STOMACH TUMOR IN RATS BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.**

Takahashi A, Onoda K, Kawashima K, Kato R, Omori Y, Ishidate M

Natl. Inst. Hyg. Sci., Tokyo, Japan

Gann; 61(3):295-296 1970

The relationship between stomach cancer and stomach ulcer was investigated by feeding a carcinogen, N-methyl-N'-nitro-N-nitrosoguanidine, to rats in which stomach ulcers had been induced by acute stress. Rats given 0, 30, or 90 mg/l of the carcinogen in drinking water but not subjected to stress did not develop any tumors in the stomach and intestine; rats receiving no carcinogen but subjected to acute stress (immobilization in a stress-cage and immersion in 23 C water for 16 hr) developed ulcers in the glandular stomach, but no tumors were observed. Solid tumors in the glandular stomach were observed in all rats subjected to stress and carcinogen treatment. One or more adenomatous hyperplastic nodules and fibrosarcomas developed in the stomach (3-6 mm diameter) and in the duodenum (5-20 mm diameter).

**105. INHIBITORY AND ENHANCING EFFECTS OF VARIOUS STRESS ON EXPERIMENTAL MAMMARY TUMORIGENESIS (MEETING ABSTRACT). (PP. 463)**

Nieburgs HE, Weiss J, Navarrete M, Grillione G, Siedlecki B

Dept Pathol, Mt. Sinai Sch Med, NY, NY 10029

Third International Symposium On Detection And Prevention Of Cancer. 1976.

Studies on the role of stress in the development of malignant neoplasms has led to conflicting reports, suggesting inhibitory and enhancing effects. The effect of stress on immunocompetence of experimental animals has been demonstrated. To elucidate the role of various types of stress on tumorigenesis, a series of basic studies on the effects of stress on the cellular level were carried out. Minute cellular changes in the thyroid, thymus, lung, liver, stomach, adrenals and testes were studies following stress from electric shock, cold swim, handling and transportation. Blood lymphocyte nuclear structures and blastogenic transformation as a result of phytoheme-agglutinin stimulation were evaluated and correlated with the effects of stress on epithelial cell changes. Experiments were designed to determine the influence of the circadian cycle, the relationship of the length of period of stress to the degree of cellular changes and duration of effects following discontinuation of stress. Marked differences in the effects of stress were noticed between two-hr and 24-hr electric shock-treated Sprague-Dawley rats 50 d old. Mitotic liver cell changes in the two-hr shocked rats were absent in the 24-hr stressed animals. In the rats after 24-hr electric shock, the cellular changes were more prominant at varying periods following discontinuation of stress than in those autopsied immediately after cessation of stress. Various types of stress led to reduced blood lymphocytes with a decrease in the percentage of small lymphocytes and relative increase in large lymphocytes. Cellular changes as a result of transportation, handling and cold swim persisted longer than those from electric shock. The role of stress on mammary tumorigenesis following intragastric administration of 40 mg DMBA in 2cc of corn oil was studied in animals treated with electric shock, cold swim and handling. Autopsies performed 90 d following administration of DMBA revealed enhancement of mammary tumor development by handling and cold swim. Electric shock failed to enhance mammary tumorigenesis and seemed to exert some inhibitory effect. (Author Abstract)

**106. THE EFFECT OF COLD STRESS ON CHEMICAL CARCINOGENESIS OF RAT SALIVARY GLANDS.**

Turbiner S, Shklar G, Cataldo E

Tufts U. Sch. Dent. Med., Boston, Mass.

Oral Surg Oral Med Oral Pathol; 29(1):130-137 1970

Pellets of 7,12-dimethylbenzanthracene were implanted in the right submandibular gland of 48 male albino rats (200-250 g) and 24 were placed in a room maintained at 3C for 19 weeks. All rats developed tumors, palpable at 11 weeks, in the right submandibular gland, but by week 13, tumors in the cold-stressed rats were larger and the rats weighed an av, of 81 g less at time of death. Microscopically, the tumors were epidermoid carcinomas and histologically similar in both groups.

## C. Effect of Stress on the Growth of Transplanted Tumors

**107. THE INFLUENCE OF STRESS AND STRESS HORMONES ON THE TRANSPLANTABILITY OF A NON-IMMUNOGENIC SYNGENEIC MURINE TUMOR.**

Peters LJ, Kelly H

Section of Experimental Radiotherapy, Univ of Texas System Cancer Center M D Anderson Hosp and Tumor Inst, 6723 Bertner Ave, Houston, TX 77030

Cancer; 39:1482-1488 1977

Quantitative transplantation assays of a syngeneic murine adenocarcinoma have been used to investigate the effects of stress hormones on tumor take probability. Cortisol, injected intraperitoneally one hour before and 3 hours after tumor cells, caused a dose dependent reduction of TD50 (number of tumor cells required for 50% takes) by factors of from 4 at a total dose 4 mug/g to 68 at 400 mug/g. ACTH, given at 0.2 IU daily for 9 days spanning the time of tumor cell injection, reduced the TD50 2.5-fold, indicating that the peak glucocorticoid level achieved, rather than its duration, was of greater significance. Adrenaline, while much less effective than cortisol, produced an 8-fold reduction in TD50 at its maximum tolerable dose. The effect of cortisol simulated that of whole body irradiation (WBI), and while both these agents depress immune reactivity, evidence is presented to suggest that immunological mechanisms are not responsible for their effect. WBI constitutes a systemic stress, and the demonstration that surgical trauma (laparotomy) could also reduce the TD50 for this tumor suggested that both might act via endogenous glucocorticoids. However, the failure of prior total adrenalectomy of mice to abrogate the effect of either WBI or laparotomy indicated that stress hormones were not essential intermediaries. It is concluded that both stress hormones, especially glucocorticoids, and stressful procedures acting independently of stress hormones, can facilitate tumor transplantation. (21 Refs) (Author Abstract)

**108. THE EFFECT OF RADIANT OR MECHANICAL STRESS AND OF STRESS HORMONES ON MURINE TUMOR TRANSPLANTABILITY (MEETING ABSTRACT).**

Peters LJ, Ayres S, McCleave H

Univ. Texas System Cancer Center, M. D. Anderson Hosp. and Tumor Inst., Section Experimental Radiotherapy, Houston, TX 77030

Radiat Res; 67(3):643 1976

Whole body irradiation (WBI) and surgical laparotomy both cause significant reductions in the T50 (number of tumor cells required for 50% takes) of a non-immunogenic murine adenocarcinoma transplanted sc. These effects produced by the administration of stress hormones at the time of assay, cortisol being more effective than adrenaline. However, prior total adrenalectomy of assay mice failed to abolish the effects

of either WBI or laparotomy. Increased plasma levels of fibrogen (a stress phase protein elevated in the absence of adrenal function) could not be correlated temporally with the effects of WBI or laparotomy. Although corticosteroids and WBI depress immune reactivity, evidence is presented to suggest that in this system, immunological mechanisms are not involved.

### 109. LOWERING OF INNATE RESISTANCE OF THE LUNGS TO THE GROWTH OF BLOOD-BORNE CANCER CELLS IN STATES OF TOPICAL AND SYSTEMIC STRESS.

Van Der Brenk HA, Stone MG, Kelly H, Sharpington C
St. Thomas' Hosp., London SE1 7EH, England
Br J Cancer; 33(1):60-78 1976

The survival and clonogenic growth of iv-injected Walker (W256) tumor cells in the lungs of specific pathogen free rats were measured in terms of colony forming efficiency. Both survival and growth were greatly enhanced by states of topical and systemic stress induced by ip injection with a single dose of 10**-5 to 10**-3 mM/g adrenaline and other b-adrenergic agonists, inflammatory agents (including local x-irradiation), convulsive seizures, "tumbling", or physical restraint. Lowering of innate resistance of the host to growth of seeded tumor cells induced by states of topical and systemic stress, and by the addition of an excess of lethally irradiated tumor cells to iv-injected intact tumor cells, was potentiated by treatment of rats with aminophylline (2-3 doses of 10**-4 mM/g, 30 min before to four hours after tumor cell injection). Enhancement of tumor growth by systemic stress was inhibited by bilateral total or medullary adrenalectomy, and is attributed to the release and actions of endogenous adrenomedullary hormones. Alpha-adrenergic and most nonadrenergic agents administered in maximum tolerated doses did not significantly affect host resistance to tumor growth in the lungs. These findings, correlated with measurements of cyclic AMP in the lungs of normal and stressed rats, suggest that changes in the resistance of the host to tumor growth involve changes in cyclic nucleotide metabolism in the target tissues (tumor bed); possible mechanisms of action of cyclic nucleotides in this respect are discussed.

### 110. CAGE CROWDING STRESS: ABSENCE OF EFFECT ON MELANOMA WITHIN PROTECTIVE FACILITIES. (MEETING ABSTRACT).

Riley V, Spackman D
Pacific Northwest Res Foundation, and Fred Hutchinson Cancer Res Center, Seattle, WA, 98104
Proc Am Assoc Cancer Res; 18:173 1977

A number of reports have described the stressful effects of cage crowding and the consequential influence upon various neoplastic processes. We employed cage crowding as a simple means for the intentional induction of chronic stress and compared the stress status and tumor behavior in mice housed singly or 2, 3, 5, 10, 15, or 20 animals per cage. Unexpectedly, no tangible differences were observed. The critical difference between our experiments and those previously reported was the protective environmental housing facilities that we employed, which minimizes the daily stress observed in conventional animal facilities. In our experiments, all the mice exhibited normal low levels of plasma corticosterone (CSR) irrespective of the number of mice per cage. CSR is a good stress index and is rapidly elevated during or following anxiety-stress. To test for the influence of cage crowding on tumor behavior, we repeated the classical Dechambre and Gosse experiment by implanting all mice with a suspension of B-16 melanoma. In contrast to their experiment, the incidence, tumor growth rate, and mouse survival times were the same for all cage populations. These data clearly demonstrate that cage crowding per se is not stressful providing that the overall housing environment is not stressful, that no males are present, fighting does not occur, and pregnancy is not a factor. (Author Abstract)

### 111. THE EFFECT OF PSYCHIC STRESS ON MICE WITH INTRAPERITONEALLY TRANSPLANTED EHRLICH ASCITIC TUMORS.

Pajntar M, Zorc M, Kalisnik M, Vraspir-Porenta O, Logonder-Mlinsek M
Institut za Histologijo in Embriologijo Medicinske Fakultete, Univerze v Ljubljani, 61105 Ljubljana, Yugoslavia
Libri Oncol; 5(2):23-29 1976

The effect of psychic stress, of the same intensity but for different periods of time, on the growth of transplanted Ehrlich ascites tumor (EAT) in mice was studied. Also, the effect of this induced stress on the adrenal glands was evaluated. Ninety-seven adult CBA mice were inoculated ip with 10' cells of EAT. The control group (A) was not exposed to stress, but the other three were: Group B, from the time of transplantation, and Groups C and D for 2 and 4 wk, respectively, before transplantation until death. The stress was induced by flashes of light followed by weak electric shocks (15-min intervals, 6 hr/day, 5 days/wk). The effect of this stress on the adrenal glands was studied over a 5-to 7.5-mo period in five female albino mice. The Group C mice lived longer than those in Group A (C:x = 16.8 days; A:x = 12.6 days; t = 2.68, P less than 0.02). The survival rate was higher among the male animals in Groups B-D, which lived 4.7 days longer than Group A males. Female mice from the experimental groups lived 3.5 days longer than female controls. The adrenal glands in the animals under stress had a significantly greater density of blood vessels in general and vacuoles in the fascicular zone, and a smaller density of giant cells in the x zone. The animals under stress lost wt, which indicates a changed equilibrium between the anabolic and catabolic hormones in favor of the latter. (11 Refs)

### 112. STRESS EFFECTS OF THE LDH-VIRUS IN ALTERING THE GARDNER TUMOR IN MICE.

Spackman D, Riley V
Pacific Nw Res. Fndn and The Fred Hutchinson Cancer Res. Center, Seattle, Wa. 98104
Proc Am Assoc Cancer Res; 16:170 1975

Since the oncogenicity of several murine viruses (Harvey, Moloney, Rauscher, Friend) has been shown to be enhanced by the LDH-virus, we have looked for similar effects with transplanted tumor cells having no known virus etiology. Twenty C3H mice were injected sc with ascites fluid containing Gardner 6C3HED lymphosarcoma cells; 10 of the mice also received simultaneously the LDH-virus. All mice developed tumors by 12 days. By 21 days, in the non-virus group, tumors in 7 of the 10 mice had regressed, with no deaths, while in the virus-infected mice, there were no regressions, and 4 of the 10 mice were dead. From day 14 to 21, the ave. tumor vol. of the virus-infected mice was 3.4 times that of the non-virus mice. This and similar experiments have shown that the virulence of transplanted Gardner tumor cells is significantly enhanced when the LDH-virus is present. This virus causes 1) an increase in tumor size, 2) a decrease in regression rates, and 3) an increase in tumor deaths, depending in part on the number of tumor cells injected. In previous studies we have shown that during the acute phase of infection with the LDH-virus there is a strong physiological 'stress' response, which includes a marked elevation of plasma corticosterone, a lymphocytopenia, and a thymus involution. Thus it is logical that the enhanced virulence of the Gardner cells, in the presence of the LDH-virus, results from a virus-hormone-mediated suppression of cellular immune responses. (Author Abstract)

**113. MELANOMA ENHANCEMENT BY VIRAL-INDUCED STRESS.**

Riley V, Spackman D

Pacific Northwest Res. Foundation and Fred Hutchinson Cancer Res. Center, Seattle, WA

Pigm Cell; 2:163-173 1976

The influence of biological stress in promoting the enhancement of tumor growth was investigated in the pigmented B-16 melanoma, a slower growing nonpigmented B-16 melanoma, and the Gardner lymphosarcoma. Biological stress was imposed by infecting tumor-bearing mice with a relatively benign murine agent, the lactate dehydrogenase-elevating virus (LDH-virus), by the direct administration of a synthetic corticoid, dexamethasone (DMS) or by controlled anxiety. The virus enhanced tumor growth and increased the percentage of lethal tumor takes following transplantation in both the Gardner lymphosarcoma and the nonpigmented B16 melanoma, but it did not affect the rapidly growing pigmented tumor. Similar effects on tumor growth were seen with DMS and the anxiety stress. All three stresses also caused a temporary increase in plasma corticosterone, followed by thymus involution and T-cell destruction. These observations indicate that experiments using mouse models for the study of immunological and neoplastic problems may be compromised by the inadvertent and unappreciated stress that is present in mice maintained in conventional facilities and handled by the usual techniques. The results also indicate that the increase of plasma corticoids that occurs during pregnancy carries risk of neoplastic enhancement. (23 Refs)

**114. EFFECT OF STARVATION OF INTACT AND ADRENALECTOMIZED MICE BEARING LYMPHOSARCOMA P1798 ON TUMOR REGRESSION AND RIBONUCLEASE ACTIVITY.**

Wiernik PH

3100 Wyman Park Dr., Baltimore, Md.

Cancer Res; 30(2):280-282 1970

In intact or adrenalectomized (adx) mice bearing established solid transplants of a corticosteroid-sensitive (CS) strain of the P1798 lymphosarcoma (about 2 cm in diameter), 1-3 d of starvation reduced tumor wt by max values of 56% and 54%, resp. In intact mice bearing a corticosteroid-resistant (CR) strain of this tumor, 1-3 d of starvation reduced tumor wt by a max of 25%. The rate of tumor wt decrease in the 3 groups was similar. As starvation continued and tumor regression occurred, tumor-specific acid RNase activity increased in the intact animals with the CS tumor, but not with the CR tumor. Tumor-specific RNase activity in adx mice with the CS tumor remained relatively unchanged. The results suggested that starvation-induced enhancement of specific RNase activity in the CS tumors may have resulted from increased endogenous corticosteroid secretion secondary to stress, but that this increased enzyme activity was not necessary for tumor regression to occur. Since both the CS and CR tumors regressed after starvation, and since adx did not prevent starvation-induced tumor regression, it is suggested that endogenous corticosteroid secretion may not mediate starvation-induced regression of the CS tumor.

**115. THE RELATIONSHIP BETWEEN CRITICAL MASS AND IMMUNOLOGICAL DEFENSE IN RAT WITH WALKER TUMOURS.**

Sforza M, Perelli-Ercolini M, Manenti A

Dept. Gen. Clin. Surg., Univ. Modena, Modena Italy

Minerva Chir; 28(22):1501-1507 1973

Walker's carcinosarcoma was implanted in albino rats, which underwent partial resection of the tumors at varying times after implantation, in some cases after being subjected to dietary deficiency, stress, or small hemorrhages. Exploratory laparotomy, partial resection (1/3 or 2/3 of tumor mass), or physiological stress after a certain period following tumor implantation (which may correspond to a critical tumor mass, in the author's view) resulted in greater mortality. Treatment with Substosan, BCG, beta-fluorene, estradiol dipropionate, and vaccinations of tumor cells reduced mortality. (21 refs)

## D. Effect of Stress on the Growth of Virus-Induced or Spontaneous Tumors

**116. THE ROLE OF PHYSIOLOGICAL STRESS ON BREAST TUMOR INCIDENCE IN MICE.**

Riley V, Spackman D, Santisteban G

Pacific Northwest Research Foundation, The Fred Hutchinson Cancer Research Center, and Seattle University, Seattle, Washington 98104

Proc Am Assoc Cancer Res; 16:152 1975

Presumed identical groups of C3H/HeJ female mice carrying the mammary tumor virus have been monitored for mammary tumor incidence while housed and handled under two different conditions in respect to exposure to chronic stress. Conventional open-rack facilities were employed for the stressed mice, whereas specially designed, protective facilities were used to minimize disquieting noises and odors, temperature fluctuations, infections, and other stress-inducing factors. Although all of the mice studied were potential candidates for virus-induced breast malignancy, the mice protected from stress exhibited only 7% tumor incidence at 12 months as compared with 92% tumors in those mice maintained under conventional stress-associated conditions. Mouse stress is expressed biochemically by an increase in plasma corticosterone which is thus used in our laboratory for detecting and quantitating stress status. Closely correlated with the elevation of this hormone is a significant decrease in circulating T-cells and an involution of the thymus. A tentative hypothesis for guidance in the further examination of these phenomena assumes that the biochemical and cellular consequences of physiological stress have adverse influences on the host surveillance systems, which thus permit a newly transformed cancer cell a greater opportunity to survive and to establish itself as a viable, irreversible neoplasm. (Author Abstract)

**117. ENHANCEMENT OF TUMOR DEVELOPMENT IN PHYSICALLY-STRESSED MICE INOCULATED WITH AN ONCOGENIC VIRUS.**

Seifter E, Rettura G, Zisblatt M, Levenson SM, Levine N, Davidson A, Seifter J

Albert Einstein Coll. Med., New York, N.Y.

Experientia; 29(11):1379-1382 1973

The effect of stress on tumor development was studied in male CBA/J mice placed in partial body casts and inoculated im with murine sarcoma virus Moloney strain (MSV-M). Partial body casting had previously been shown to induce moderate stress manifested by decreased thymus and spleen size and increased adrenal gland size. With all inoculation doses except the highest (1 x 10-1), stressed mice had a higher incidence of tumor formation than did nonstressed MSV-M inoculated control mice. The latency period for tumor development was dose-related in both groups but was decreased in stressed animals compared to controls. Maximum tumor size was greater and the rate of subsequent tumor regression was slower in stressed mice.

**118. MOUSE MAMMARY TUMORS: ALTERATION OF INCIDENCE AS APPARENT FUNCTION OF STRESS.**

Riley V

Dept. of Microbiology, Pacific Northwest Res. Foundation, and Fred Hutchinson Cancer Res. Center, Seattle Washington 98104

Science; 189(4201):465-467 1975

The effect of different experimental and environmental conditions on mammary tumor incidence and latency was studied in C3H/He mice carrying the Bittner strain of mammary tumor virus. Form 80-100% of these mice usually develop mammary tumors within 8-18 mo after birth when studied under the usual housing and experimental conditions. Four groups of mice were investigated: parous mice housed under conditions of chronic environmental and manipulative stress (group A); nonparous mice housed under the same conditions of chronic environmental and manipulative stress (group B); nonparous mice housed under protective conditions and subjected to moderate intermittent stress (group C); and mice provided with maximum protection from environmental and manipulative stress (group D). The last group was a combination of parous, nonparous, and virgin mice delivered by cesarean section and foster-nursed to deplete the milk-passaged tumor virus. The median tumor latency period for group A was 276 days compared with 358 days for group B. In group C the median latency period was 566 days, a significant extension over both groups A and B. At 400 days of age, the incidence of spontaneous mammary tumors was 92% in group A, 60% in group B, and 7% in group C. Group D had no such small tumor incidence that determination of a median latency period was not possible. At 21 mo of age, one mammary tumor was detected in 75 surviving mice. The data suggest that moderate chronic or intermittent stress may predispose C3H/He mice to an increased risk of mammary carcinoma, possibly through a resultant compromise of their immunological competence or tumor surveillance system, and that adequate protection from physiological stress may reduce the occurrence of the mammary tumors.

### 119. MODIFYING EFFECTS OF A BENIGN VIRUS ON THE MALIGNANT PROCESS AND THE ROLE OF PHYSIOLOGICAL STRESS ON TUMOR INCIDENCE. (pp. 319-336)

Riley V, Spackman D

Modulation of Host Immune Resistance in the Prevention or Treatment of Induced Neoplasias. NCI and John E. Fogarty International Center for Advanced Study in the Health Sciences, Bethesda, MD, 1977.

The ip administration of lactate dehydrogenase (LDH) virus, which is a benign passenger in most classical transplantable mouse tumors and oncogenic virus preparations, elevated corticosterone levels significantly in three strains of 6-to 10-wk-old female mice. These elevations apparently caused thymus involution and lymphocytopenia. When LDH virus was administered together with oncogenic viruses, tumor growth was significantly enhanced, presumably because of a decrease in cell-mediated immunity. In genetically susceptible C3H/HeJ female mice carrying the Bittner mammary tumor virus from birth, tumor incidence was dramatically reduced from about 90% in mice housed under sustained stress to less than 10% in mice housed in plastic cages held in specially designed protective, enclosed, ventilated shelves that minimize stress induction. The data suggest that social and physiological stress may compromise immunological competence and thus enhance malignancy. Reexamination of earlier experimental data on tumor induction in mice is recommended. (102 Refs)

### 120. MALIGNANCY OF POLYOMA VIRUS INFECTION IN MICE IN RELATION TO STRESS.

Rasmussen AF, Hildemann WH, Sellers M

Dept. Infect. Dis, U. Calif. Sch. Med., Los Angeles

J Natl Cancer Inst; 30(1):101-112 1963

Webster-Swiss (BRVS) mice (135) inoculated at birth (intracardiac route) with polyoma virus, then systemically stressed by avoidance learning or high frequency sound beginning 5-6 wk later, and observed for 487 days showed no significant difference from their (69) unstressed controls in the over-all incidence, extent or location of tumors, in survival time, or in the development of hemagglutination-inhibition antibodies. However, the frequency of overt tumors was slightly diminished in the unstressed mice (probably not significantly). The virus-induced malignancies reduced the median lifespan by at least two-thirds in all groups, and the cumulative mortality curves all showed the same log-normal distribution though the wide range of survival time (56-415 days) reflects a highly variable disease process. The non-tumorous survivors (3 stressed, 2 unstressed) all showed high titers of antibodies. Of the tumor-bearers, 81% had multiple tumors at death, and tumors of salivary gland and lung were most frequent (62-65%), while kidney, skeletal, and sc tumors were found in 20%, 23% and 19% resp. The lack of effect of stress on malignancy might be due to the time lag between virus inoculation and stress application, the virus-induced neoplastic transformation being presumably accomplished before stress application.

### 121. THE INFLUENCE OF STRESS ON MURINE LEUKEMIA VIRUS INFECTION (MEETING ABSTRACT).

Jensen MM

U. California Los Angeles, Sch. Med., Los Angeles, CA 90024

Proc Soc Exp Biol Med; 127(2):610-614 1968

Various stresses were inflicted on 6-8-wk-old inbred female Swiss Webster-BRVS mice inj with Rauscher leukemia virus (RLV). Mice subjected to 10 daily periods of sound stress or to avoidance-learning stress before iv inj of RLV showed a significant retardation of splenic enlargement. Another group showed significant retardation in spleen size when stress was applied after, but not before, inoc of RLV. The difference in mean wt between stressed (20.9 g) and control (21.3 g) mice was significant. In another group subjected to avoidance-learning stress (for 5 days), followed by adrenalectomy (adx) and a 1-day rest before RLV inj. (iv) with RLV, then stressed again (for 13 days) and sacrificed, a significant difference in spleen size was seen between stressed and control intact mice, but not between stressed and control adx mice. Death rates were lower in stressed mice. No correlation was observed between the effectiveness of stress and splenic colony-forming titers, plasma virus contents or splenic histology. No significant differences were seen between intact and adx infected mice, when both groups were treated sc with 6-mercaptopurine (30 mg/kg/inj), triethylene melamine (0.5 mg/kg) or a terephthalanilide compound (50 mg/kg) at 2-day intervals through day 16 after FLV inoc.

### 122. INHIBITION OF MURINE SARCOMA DEVELOPMENT BY DEOXYCORTICOSTERONE ACETATE.

Seifter E, Rettura G, Demetriou AA, Levenson S, Rahman S, Seifter J

Dept. Biochem. Surg., Albert Einstein Med. Coll., Bronx, N.Y.

J Natl Cancer Inst; 53(6):1809-1812 1974

Results of the effect of 11-deoxycorticosterone acetate (100 ug/d po in food) on tumor development and growth in male CBA/J and female C3H/HeJ mice either subjected to physiologic stress or inoculated with murine sarcoma virus are presented. Steroid treatment was initiated on the same d as virus inoculation or stress body casting; animals were sacrificed after 3 d. Deoxycorticosterone-treated, unstressed mice showed more wt gain (1.4 g vs 0.2 g) whereas treated, stressed mice lost less wt. (1.9 g vs 3.5 g) than their respective controls. Steroid treatment partially prevented stress-induced thymus involution and spleen wt loss as well as augmented stress-induced wt loss of inguinal nodes. Fewer murine

sarcoma virus-inoculated, deoxycorticosterone-treated CBA/J mice developed tumors (30-65%) than did controls (90-100%). Steroid treatment extended the latency period for tumor development by 2.4-3.4 d and resulted in more rapid and complete tumor regression than in controls. Similar results were obtained with C3H/HeJ mice. 11-Deoxycorticosterone has been shown to accumulate in metyrapone-treated mice and it is concluded from the present experiments that deoxycorticosterone accounts for at least part of the antitumor activity of metyrapone. (27 refs)

**123. APPARENT INHIBITORY INFLUENCE OF STRESS ON SJL/JDG NEOPLASIA.**

Crispens CG
Dept. Biology, Univ. Alabama in Birmingham, Birmingham, AL 35294
IRCS Med Sci: Cancer; 4(4):169 1976

The influence of stress on the development of type B reticulum cell sarcomas in male SJL/JDg mice was investigated. At 5 wk of age, weanling males were caged singly and collectively (three animals per cage). Body and adrenal weights of males were compared with similar data for females held under routine caging conditions (four animals per cage). Adrenal weights in females were higher (22.1, 22.4, and 15.7 mg/100 g body weight after 6, 30, and 52 wk, respectively) than those for males caged singly (8.8, 7.6, and 6.9 mg/100 g after 6, 30, and 52 wk, respectively) or for males caged collectively (9.0, 11.9, and 16.2 mg/100 g after 6, 30, and 52 wk, respectively). Female adrenals decreased in size with age. Adrenals in males caged collectively were larger than in males caged singly, exhibited a progressive increase in size, and attained a mean weight equal to that of females at 52 wk of age. The data support the assumption that males caged collectively are exposed to a higher level of environmental stress than singly-caged males. The incidence of sareoma in males caged collectively (1/17 at 30 wk and 5/18 at 52 wk of age) was significantly lower than that for males caged singly (6/15 at 30 wk and 17/27 at 52 wk), suggesting an inhibitory influence of stress on the development of spontaneous reticulum cell neoplasms in SJL/JDg mice. A reduction in the level of exposure to stress did not entirely eliminate the difference in tumor incidence between the sexes, however; males caged singly showed tumor incidences of 40 and 63% at 30 and 52 wk, respectively, as compared to female incidences of 64 and 86%, respectively. Treatment with corticosteroids is suggested as a possible means for retarding the development of SJL/JDg neoplasms. (5 refs)

**124. THE POSSIBLE EFFECT OF METEOROLOGICAL STRESS ON CANCER AND ITS IMPORTANCE FOR PSYCHOSOMATIC CANCER RESEARCH.**

Tromp SW
Biometerol. Res. Cent. Leiden, Netherlands
Experientia; 30(12):1474-1478 1974

Meteorological stresses may affect neoplastic diseases in the same way as do psychological stresses. Several meteorological factors could affect the normal physiological processes in the human body (e.g, thermal stimuli, humidity, solar radiation, air movement, partial oxygen pressure). The effects of these stimuli depend on the time of day, the experimental history, the degree of acclimatization to the physical environment, the psychological and anatomical typology of the subject. Through the intermediary of the hypothalamus, long lasting, meteorological stresses could have a profound influence on the hormonal processes in the human body. Various research studies have shown correlations between mean annual temperature, season of the yr, season of the yr at birth, and the incidence of various types of cancer. Other studies have correlated the growth of various tumors with variations in the ambient temperature. Low pressure treatment was found to markedly inhibit the growth of tumors in rats, and adrenalectomy abolished this effect; susceptibility to cancer development after tumor transplantation in rats was also correlated with atmospheric pressure. Since temperature and humidity affect virus development and the general body resistance to infections, the antibody level of the serum, soil, weather, and climate could also influence carcinogenic processes induced by viruses.

**125. EXPERIMENTAL AND ENVIRONMENTAL FACTORS IN CANCER. A REVIEW OF RESEARCH WITH ANIMALS.**

LaBarba RC
U. South Florida, Tampa
Psychosom Med; 32(3):259-276 1970

A review of animal research relating experiential or environmental factors to the etiology and pathogenesis of neoplastic disease includes studies of crowding, exercise, early experience (handling, immobilization, deprivation, maternal separation), stress (electric shock, avoidance conditioning, fearful exposure), and Soviet research (i.e the effect of experimentally-induced neurosis on cancer development). The resulting empirical evidence concludes that response to cancer can be influenced by experiential and/or environmental manipulation. Additional research efforts by psychologists are scientifically justified.

# SUBJECT INDEX


Anti-inflammatory Agents, 10, 75, 78
Cancer-prone Personality (see also Psychological Factors in Carcinogenesis)
  life-style, 19, 24, 31, 34, 36, 45, 54
  personality, 3, 28-30, 37-51, 54
  psyche, 39, 50, 63, 64
  psychosomatic factors, 32, 33, 41, 42, 44, 49, 50, 54
Experimental Tumorigenesis
  burns, 82
  cage conditions, 69-73, 103, 116, 118, 119, 123
  cold, 96, 99, 105, 106
  crowding, 94, 110, 125
  electric shock, 71, 89, 90, 92, 94, 95, 103, 105, 111, 125
  environmental stress, 97-100
  exercise, 91, 100, 125
  handling, 69, 70, 72, 95, 105, 118, 125
  light, 101, 111
  meteorological stress, 124
  motion, 102
  nutritional stress, 71, 77, 115
  radiation, 96-98, 107, 108
  restraint, 67, 68, 88-91, 103, 104, 109, 117, 122
  sound stress, 90, 93, 94, 120-122
  surgical stress, 74, 107, 108, 115
  starvation, 87, 114
  transportation, 105
  viruses, 81, 82, 84, 85, 112, 113, 116-125
Immunological Factors
  host resistance, 116
  immunity, 4, 28, 58, 59, 63, 77, 81, 105, 107, 108, 112, 115, 118, 119
  immunoglobulins, 57, 58, 71
  immunological factors, 29, 31, 32, 54, 69-72, 76-79
  T-cells, 55, 58, 69, 70, 72, 113, 116
  thymus, 55, 69-73, 76, 79, 80, 84, 85, 112, 113, 116, 117, 119, 122
  spleen, 55, 69
  lymph nodes, 55, 69
Neoplasms
  cervical, 1, 6-8, 15-18, 22, 23, 34, 35, 39, 41
  endometrial, 17, 41
  epidermoid, 106
  gastric, 35, 46, 104
  gastrointestinal, 58
  hepatic, 101, 102
  Hodgkin's disease, 9, 11
  leukemia, 8, 9, 11, 32, 35, 43, 94
  lymphoma, 8, 53, 58, 114
  lymphosarcoma, 113
  mammary, 1-4, 14, 21, 28, 30, 35, 37-39, 41, 46, 52, 56, 57, 61, 62, 103, 105, 116, 118, 119
  melanoma, 110, 113
  ovarian, 35, 41
  pancreatic, 11, 19, 20, 25
  pulmonary, 11-13, 35, 40, 46, 48, 86
  sarcoma, 9, 123
  other, 11, 41, 106, 120
Neuroendocrinological Factors
  adrenal gland, 55, 68, 80, 84, 85, 88, 90, 91, 96, 102, 103, 111, 114, 117, 121, 123, 124
  adrenaline, 95, 107-109, 121
  autonomic system, 33, 63
  corticosteroids, 2, 55, 56, 62, 66, 68-70, 72-76, 79, 85, 93, 103, 108, 110, 112, 113, 116, 119, 122
  cortisol, 59, 61, 107, 108
  glucocorticoids, 80, 82, 86, 107
  hormonal factors, 4, 25, 29, 42, 54, 66-76, 78, 79, 111
  hypothalamus, 59, 63, 67, 71
  nervous system, 31, 32
  neuroendocrine system, 55, 63, 64, 90, 92, 103
  pituitary, 59, 65, 67, 68, 89, 102
  steroid hormones, 5, 16, 56, 62
Pregnancy, 4, 7, 67, 73, 113
Psychological Factors in Carcinogenesis (See also Cancer-prone Personality)
  affective disorders, 27, 29-36
  alienation, 29, 32
  anger, 37, 57
  anxiety, 8, 29, 35, 113
  behavior, 23, 24, 32, 54
  depression, 2, 8, 11, 27, 29-31, 35-37, 41, 46, 54
  despair, 32-34, 41, 44, 54
  ego defenses, 38, 56
  emotional stability, 6, 35
  emotional stress, 2-13, 29, 33, 35, 37, 39, 44, 46, 55, 58, 61, 62, 71, 75
  emotional expression, 37, 40, 43, 51, 57
  extroversion, 40
  hostility, 38
  isolation, 32
  life-event stress, 1, 8, 22, 34, 41, 45
  loss, 22, 29-33, 41, 42, 44
  mental illness, 39
  neuroticism, 8, 27, 30, 40
  psychological factors, 9, 31
  self-hatred, 42
Risk Factors Combining with Stress
  alcohol, 10, 16, 26, 28, 36, 54, 65, 75
  childhood, 32, 34, 40, 43-47
  diet, 4, 25, 28, 36, 61
  divorce, 14, 15, 17-22
  education, 6, 43
  genetic factors, 4, 10-13, 18-21, 46, 53, 87
  poverty, 18
  psychosocial factors, 1, 9, 43, 45-47, 63
  religion, 16, 20, 21
  sexuality, 6, 16, 20, 22, 23, 25, 28, 34, 39
  sociocultural factors, 20, 24
  socioeconomic level, 4, 10, 15, 20, 22, 30, 38
  widowhood, 14-16, 18, 21, 44

tobacco, 10, 12, 13, 16, 28, 36, 40, 54
Rorshach Test, 9, 43, 48-50
Screening Program, 45-54
Stress-related Diseases
autoimmune arthritis, 71, 77
cardiovascular, 8, 66, 69
coronary, 3, 5, 29
psychiatric, 26, 28
schizophrenia, 26, 28, 30, 71
ulcer, 10, 104
ulcerative colitis, 58, 75
Viral Factors, 4, 15, 25, 53, 55, 116-122
Vitamins
A, 12, 70, 80-86
E, 87

# AUTHOR INDEX WITH CITATION NUMBERS


Ackman P....56
Aleksandrowicz....43
Amkraut AA....71
Anderson MR....95
Austarheim K....50
Ayres S....108
Bagshaw MA....19
Bahnson CB....29, 45, 47
Bahnson MB....45, 47
Baker DG....97, 98, 99
Bako G....14
Baldwin JA....27
Baltrusch E....50
Baltrusch HJ 1, 9, 50, 54, 64
Beck D....44
Bennett LR....96
Billing MS....96
Blaser P....44
Blohmke M....46, 47
Brooks SC....62
Brown JH....31
Brozek A....43
Bunge EC....83
Burch P....13
Carter AC....61
Cataldo E....106
Ch'eng Feng-Lin....7
Clarke M....15
Clarkin J....41
Cockett AT....19
Cooley B....103
Cooper E....41
Cooper WC....77
Cramer I....46, 47
Crispens CG....123
Critselis AN....86
Davidson A....117
Deguire K....41
Demetriou AA....122
Dennis M....72
DeLuca HF....83
Diamond E....20
Dil'man VM....59
Dilman VM....60
Dutz W....58
Elie R....79
Erdely E....48
Evans NJ....27
Farlin M....61
Feldman EB....61
Fernandes G....77
Fitzmaurice MA....72
Ford L....22
Fox BH....23
Fritzsche U....32
Fuller JL....94
Gala RR....68
Gallagher TF....56
Gambino JJ....96
Garcia D....30
Gath D....27
Gildow J....88
Gillies M....10
Glass GB....75
Gomez R....30
Good RA....77
Goodwin BJ....16
Goulis K....26
Graham JB....22
Graham S....22
Greer HS....37, 52
Greer S....57
Grgurevic M....16
Grillione G....105
Grytting A....72
Hansen MA....77
Hellman L....56
Henry JP....103
Herberger W....35
Hildemann WH....120
Hollander CF....97
Hurst MW....8
Ishidate M....104
Jahn A....97
Jenkins CD....8
Jensen MM....121
Jose DC....77
Kaczanowski K....43
Kalisnik M....111
Kaliss N....94
Karaiossefidis....26
Kasper P....71
Kato R....104
Katz JL....56
Kawashima K....104
Kegeles SS....24
Kelepouris M....26
Kelly H....107, 109
Kepinski A....43
Kessler II....16
King H....20
Kissen DM....40
Kohout E....58
Konig U....44
Kovacs K....91
Kralova A....6
Kramer TR....77
Kravtsova EL....74
Kulcar Z....16
Labrum AH....34
Lamson BG....96
Lapp WS....79
Lask M....3
Lazere F....93
LaBarba RC....125
Lees AW....14
Lefkon BW....61
Leis HP....4
Lerer SB....30
Levendel L....48
Levenson S....122
Levenson SM ..81, 84, 117
Levine N....117
Levine NS....82
Lewis JL....41
Lilienfeld AM....20, 21
Litvai G....48
Liu Chih-Ming....7
Liu T'ung-Hua....7
Logonder-Mlinse....111
Manenti A....115
Martin du Pan R....28
Mason AD....82
Mastrovito RC....41
McClanahan H....55
McCleave H....108
Meites J....67
Mendez JL....30
Meyer R....44
Mezei A....48, 49
Miller TR....63
Modan B....17
Molomut N....93
Morris T....52
Mosinger M....53
Muller C....28
Murphy GM....19
Navarrete M....105
Nemeth G....11, 49
Newberry BH....88, 89
Newell GR....18
Nieburgs HE....105
Omori Y....104
Onoda K....104
Oo M....11
Packer L....87
Pajntar M....111
Peacock PB....36
Pellanda EB....66
Perelli-Ercolin....115
Peters LJ....107, 108
Pettingale KW....52, 57
Pradhan SN....90, 92
Pruitt BA....82
Raciti A....4
Rahman S....122
Rasmussen AF....120
Rassidakis NC....26
Ray P....90, 92
Reese RL....88
Rettura G81, 84, 86, 117, 122
Reznikov AG....74
Rhamy RK....19
Richards MC....38
Riegle GD....67
Riley V55, 69, 70, 72, 73, 110, 112, 113, 116, 118, 119
Ringel E....33
Rose RM....8
Rossipal E....58
Rothwax Y....56
Rotkin ID....25
Ryan K....52
Ryhiner O....44
Sachar EJ....56
Sakakibara T....101
Salisbury RE....82
Santisteban G....72, 116
Santisteban GA....55, 69
Scardino PL....19
Scherg H....46, 47
Schittek A....81
Schlesinger M....76
Schmahl D....100
Schottenfeld D....21
Scribner JD....78
Seifter E80, 81, 82, 84, 85, 86, 117, 122
Seifter J....117, 122
Sellers M....120
Sforza M....115
Shane M....31
Shani M....17
Sharon Z....17
Sharpington C....109
She Ming-P'eng....7
Shklar G....106
Siedlecki B....105
Silva JL....30
Simpson JS....52
Sirtori C....12
Skyring A....10
Slaga TJ....78
Slomiany BL....75
Smith LW....93
Smith SW....68
Snell LM....22
Solomon GF....71
Somogyi A....91
Spackman D55, 69, 73, 110, 112, 113, 116, 119
Spackman DH....72
Stancliff EK....18
Stephens PM....103
Stoll BA....2
Stone MG....109
Strand M....16
Styk J....44
Surawicz FG....39
Suzuki S....102
Takahashi A....104
Tashima C....5
Tee DE....57
Tenney VA....42
Toews J....31
Tromp SW....124
Ts'ai Hai-Ying....7
Turbiner S....106
Van Der Brenk H....109
Varsamis J....31
Vessal K....58
Vraspir-Porenta....111
Walker HL....82
Weiner H....56
Weinhold M....47
Weinzweig N....84
Weiss J....105
Wiernik PH....114
Wogon J....88
Wu Ai-Ju....7

Yunis EJ .....77
Zanoboni A .....65
Zanoboni-Muciac .....65
Zilc M .....83
Zimolo A.....16
Zisblatt M .....117
Zorc M .....111
Zurowska A .....43

INTERNATIONAL CANCER RESEARCH DATA BANK

# cidac*

## INFORMATION SHEET

The International Cancer Research Data Bank (ICRDB) Program has established three CIDACs for promoting dissemination of cancer information, each specializing in a broad area of cancer research. These are staffed by scientists and consultants who have a thorough and detailed understanding of the subject areas covered by the particular CIDAC.

The CIDACs provide active dissemination of cancer research information to scientists and act as reference and referral centers for investigators. CIDACs offer two major types of service:

> Current Awareness Service ("CANCERGRAMS") - Regularly published collections of abstracts of newly published results in specific cancer research areas; 60-80 topics will be covered with automatic distribution every few weeks to researchers working in areas corresponding to a CANCERGRAM topic.
>
> Oncology Overviews - Comprehensive listings of abstracts of papers published in recent years on selected high-interest subjects of special interest to researchers; approximately 30 topics will be covered each year.

Additionally, each CIDAC identifies ways to optimize methods for indexing, retrieving, and summarizing scientific information and findings. CIDACs will also identify and implement new projects to promote exchange of technical information between cancer researchers on a worldwide basis.

The addresses of the CIDACs are:

CIDAC for Carcinogenesis
(John S. Krebs, Ph.D., Director)
Stanford Research Institute
333 Ravenswood Avenue, Bldg. 100
Menlo Park, California 94025

CIDAC for Cancer Therapy
(Eugene M. McKelvey, M.D., Director)
M.D. Anderson Hospital and Tumor Institute, CP608
6723 Bertner Avenue
Houston, Texas 77030

CIDAC for Cancer Virology, Immunology and Biology
(Graham LeM. Campbell, Ph.D., Director)
Franklin Institute Research Laboratories
20th and Race Streets
Philadelphia, Pennsylvania 19103

7704

*A service of the International Cancer Research Data Bank (ICRDB)
National Cancer Institute
Room 128, Blair Building, Bethesda, Md. 20014